FORM PTO-1390 (REV. 11-2000) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER	U.S. APPLICATION NO. (If known, see 37 CFR 1.5)
0425-0847P	09/913444 NEW

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/JP00/00799	February 15, 2000	February 15, 1999

TITLE OF INVENTION

HETERODIAZINON COMPOUND

APPLICANT(S) FOR DO/EO/US

ITO, Koichi; KITAZAWA, Noritaka; NAGATO, Satoshi; KAJIWARA, Akiharu; FUKUSHIMA, Tatsuto; HATAKEYAMA, Shinji; HANADA, Takahisa; UENO, Masataka; UENO, Kohshi; KAWANO, Koki

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39 (1).
4. ☒ The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☒ has been transmitted by the International Bureau. WO 00/47567
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☒ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. ☒ is transmitted herewith.
   b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4)
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3)).
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)). **(Original)**
10. ☐ An English language translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 20. below concern document(s) or information included:

11. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98./International Search Report (PCT/ISA/210) and PTO-1449
12. ☒ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☒ A FIRST preliminary amendment.
14. ☐ A SECOND or SUBSEQUENT preliminary amendment.
15. ☐ A substitute specification.
16. ☐ A change of power of attorney and/or address letter.
17. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821-1.825.
18. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).
19. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
20. ☒ Other items or information:
    1.) Zero (0) sheets of Formal Drawings
    2.) PCT Substitute Sheets Letter w/ Amended Abstract

U.S. APPLICATION NO (if known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO	ATTORNEY'S DOCKET NUMBER
09/913444	PCT/JP00/00799	0425-0847P

21. ☒ The following fees are submitted:

	CALCULATIONS	PTO USE ONLY
BASIC NATIONAL FEE (37 CFR 1.492(a)(1)-(5):		
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO **$1,000.00**		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO **$860.00**		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO. **$710.00**		
International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) **$690.00**		
International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4). **$100.00**		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 860.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$ 0	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total Claims	47 - 20 =	27	X **$18.00**	$ 486.00	
Independent Claims	3 - 3 =	0	X **$80.00**	$ 0	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)		Yes	+ **$270.00**	$ 270.00	
TOTAL OF ABOVE CALCULATIONS =				$ 1616.00	
☐ Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2.				$ 0	
SUBTOTAL =				$ 1616.00	
Processing fee of **$130.00** for furnishing the English translation later than ☐20 ☐30 months from the earliest claimed priority date (37 CFR 1.492(f)). +				$ 0	
TOTAL NATIONAL FEE =				$ 1616.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +				$ 40.00	
TOTAL FEES ENCLOSED =				$ 1656.00	
				Amount to be: refunded	$
				charged	$

a. ☒ A check in the amount of $ **1656.00** to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. _____ in the amount of $_____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 02-2448.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

Send all correspondence to:
Birch, Stewart, Kolasch & Birch, LLP or Customer No. 2292
P.O. Box 747
Falls Church, VA 22040-0747
(703)205-8000

Date: August 15, 2001

By _____
Raymond C. Stewart, #21,066

/tf

PATENT
0425-0847P

IN THE U.S. PATENT AND TRADEMARK OFFICE

Applicant:	ITO, Koichi et al	Conf.:	
Int'l. Appl. No.:	NEW		
Appl. No.:	PCT/JP00/00799	Group:	
Filed:	August 15, 2001	Examiner:	
For:	HETERODIAZINON COMPOUND		

PRELIMINARY AMENDMENT

BOX PATENT APPLICATION
Assistant Commissioner for Patents
Washington, DC 20231

August 15, 2001

Sir:

The following Preliminary Amendments and Remarks are respectfully submitted in connection with the above-identified application.

AMENDMENTS

IN THE SPECIFICATION:

Please amend the specification as follows:

Before line 1, insert --This application is the national phase under 35 U.S.C. § 371 of PCT International Application No. PCT/JP00/00799 which has an International filing date of February 15, 2000, which designated the United States of America.--

IN THE CLAIMS:

Please amend the claims as follows:

10. (Amended) The heterodiazinon compound according to claim 7 represented by the following formula (IV):

(IV)

(wherein R^1 and R^2 have the same meanings as defined above), a pharmacologically acceptable salt thereof or hydrates thereof.

11 (Amended) The heterodiazinon compound according to claim 7, a pharmacologically acceptable salt thereof or hydrates thereof, wherein the aryl group is a group selected from phenyl group, indenyl group, naphthyl group, azulenyl group, heptalenyl group and anthnyl group; the heteroaryl group is a group selected from thienyl group, furyl group, pyranyl group, pyrrolyl group, imidazolyl group, pyrazolyl group, triazolyl group, tetrazolyl group, isothiazolyl group, thiazolyl group, thiadiazolyl group, isoxazolyl group, pyridyl group, pyrazinyl group, pyrimidyl group, pyridazinyl group, indolizinyl group, isoindolyl group, indolyl group, indazolyl group, isoquinolyl group, quinolyl group,

phthalazinyl group, naphthylidinyl group, quinoxalinyl group quinazolinyl group and cinolynyl group; and the lower cycloalkyl group is a group selected from cyclopropyl group, cyclobutyl group, cyclopentyl group, cyclohexyl group, cycloheptyl group and cycloctyl group.

12. (Amended) The heterodiazinon compound according to claim 7, which is the compound selected from the following compounds or pharmacologically acceptable salts thereof or hydrates thereof.

(1) 2-(2-Pyridyl)-4- phenyl-4H-1,3,4- oxadiazine-5 (6H)-one,

(2) 2-(2-Pyrazinyl)-4-phenyl-4H -1,3,4-oxadiazine-5 (6H) -one,

(3) 2-(1-methyl-2-pyrolyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(4) 2,4-diphenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(5) 2-(2,3-dimethoxyphenyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(6) 2-(2-pyrrolyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(7) 2-(2-quinolyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(8) 2-(6-methyl-2-pyridyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(9) 2-benzoyloxymethyl-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(10) 2-(2-pyridyl)-4-(2,4-difluorophenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(11) 2-(2-pyridyl)-4-cyclohexyl-4H-1,3,4-oxadiazine-5(6H)-one,

(12) 2-(2-chloro-4-pyridyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(13) 2-(3-methoxy-2-pyridyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(14) 2-(3-hydroxy-2-pyridyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(15) 2-styryl-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(16) 2-[2-(3-pyridyl)vinyl]-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(17) 2-(2-methoxyphenyl)-4-(2-bromophenyl)-4H-1,3,4-oxadiazine-5 (6H)-one,

(18) 2-(4-nitrophenyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(19) 2-(3-nitrophenyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(20) 2-(2-nitrophenyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(21) 2-(4-morpholinyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-

one,

(22) 2-cyclohexyl-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(23) 2-dimethylamino-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(24) 2-dimethylamino-4-phenyl-4H-1,3,4-thiadiazine-5(6H)-one,

(25) 2-(2,6-dimethoxyphenyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(26) 2-(2-methoxyphenyl)-4-(2-fluorophenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(27) 2-phenyl-4-cyclohexyl-4H-1,3,4-oxadiazine-5(6H)-one,

(28) 2-(2-methoxyphenyl)-4-cyclohexyl-4H-1,3,4-oxadiazine-5(6H)-one,

(29) 2-(3-pyridyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(30) 2-phenyl-4-(2-bromophenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(31) 2-(2-thienyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(32) 2-benzyl-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(33) 2-(2-pyridyl)-4-(2-bromophenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(34) 2-(2-pyridyl)-4-(2-fluorophenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(35) 2-(2-pyridyl)-4-(2-methoxyphenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(36) 2-phenyl-4-(2-cyanophenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(37) 2-phenyl-4-(2-nitrophenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(38) 2-phenyl-4-(2-pyridyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(39) 2-phenyl-4-(3-pyridyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(40) 2-phenyl-4-(3-cyano-2-pyridyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(41) 2-phenyl-4-(2-hydroxymethylphenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(42) 2-phenyl-4-(2-cyano-3-pyridyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(43) 2-phenyl-4-(2-thienyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(44) 2-phenyl-4-(3-thienyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(45) 2-phenyl-4-(4-cyanophenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(46) 2-phenyl-4-(3-cyanophenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(47) 2-phenyl-4-(2-cyano-3-thienyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(48) 2-(2-hydroxyphenyl)-4-(2-bromophenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(49) 2-(2-hydroxyphenyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(50) 2-phenyl-4-(2-hydroxyphenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(51) 2-(2-hydroxyphenyl)-4-(2-fluorophenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(52) 2-(2-hydroxyphenyl)-4-(4-fluorophenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(53) 2-(2-hydroxyphenyl)-4-(2,4-difluorophenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(54) 2-[2-(2-dimethylamino)ethoxyphenyl]-4-(2-bromophenyl)-4 H-1,3,4-oxadiazine-5(6H)-one,

(55) 2-[2-(4-pyridyl)methoxyphenyl]-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(56) 2-{2-[2-(4-morpholinyl)ethoxy]phenyl}-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(57) 2-[2-(2-pyridyl)methoxyphenyl]-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(58) 2-[2-(3-pyridyl)methoxyphenyl]-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(59) 2-{2-[2-(1-piperidyl)ethoxy]phenyl}-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(60) 2-{2-[2-(1-pyrrolidinyl)ethoxy]phenyl}-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(61) 2-[2-(2-dimethylaminoethoxy)phenyl]-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(62) 2-[2-(3-dimethylaminopropoxy)phenyl]-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(63) 2-{2-[3-(1-piperidinyl)propoxy]phenyl}-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(64) 2-phenyl-{4-[2-(4-morpholinyl)ethoxy]phenyl}-4H-1,3,4-oxadiazine-5(6H)-one,

(65) 2-phenyl-4-[2-(2-dimethylaminoethoxy)phenyl]-4H-1,3,4-oxadiazine-5(6H)-one,

(66) 2-[2-(2-dimethylaminoethoxy)phenyl]-4-(2-fluorophenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(67) 2-{2-[2-(4-morpholinyl)ethoxy]phenyl}-4-(2-fluorophenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(68) 2-{2-[2-(4-morpholinyl)ethoxy]phenyl}-4-(2-bromophenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(69) 2-{2-[2-(4-morpholinyl)ethoxy]phenyl}-4-cyclohexyl-4H-1,3,4-oxadiazine-5(6H)-one,

(70) 2-{2-[2-(4-morpholinyl)ethoxy]phenyl}-4-(4-fluorophenyl)-4 H-1,3,4-oxadiazine-5(6H)-one,

(71) 2-{2-[2-(4-morpholinyl)ethoxy]phenyl}-4-(2,4-difluorophenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(72) 2-[3-(2-hydroxyethoxy)-2-pyridyl]-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(73) 2-{3-[2-(4-morpholinyl)ethoxy]-2-pyridyl}-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(74) 2-{3-[2-(1-piperidyl)ethoxy]-2-pyridyl}-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(75) 2-{3-[2-(1-pyrrolidinyl)ethoxy]-2-pyridyl}-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(76) 2-{3-[2-(1-methyl-2-pyrrolidinyl)ethoxy]-2-pyridyl}-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(77) 2-[3-(2-dimethylaminoethoxy)-2-pyridyl]-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(78) 2-(3-aminophenyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(79) 2-(2-aminophenyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(80) 2-phenyl-4-(tetrahydro-4H-pyran-4-yl)-4H-1,3,4-oxadiazine-5(6H)-one,

(81) 2-phenyl-4-(1-methyl-4-piperidyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(82) 2-phenyl-4-(3-quinuclidinyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(83) 2-pyridyl-4-(1-benzyl-4-piperidyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(84) 2-phenyl-4-(3-tetrahydrofuranyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(85) 2-phenyl-4-cyclopentyl-4H-1,3,4-oxadiazine-5(6H)-one,

(86) 2-phenyl-4-(1-benzyl-4-piperidyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(87) 2-phenyl-4-[1-(2-pyridyl)ethyl]-4H-1,3,4-oxadiazine-5(6H)-one,

(88) 2-phenyl-4-[1-(3-pyridyl)ethyl]-4H-1,3,4-oxadiazine-5(6H)-one,

(89) 2-phenyl-4-[1-(4-pyridyl)ethyl]-4H-1,3,4-oxadiazine-5(6H)-one,

(90) 2-(3-dimethylaminophenyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(91) 2-(2-dimethylaminophenyl)-4-phenyl-4H-1,3,4-

oxadiazine-5(6H)-one,

(92) 2-[2-(4-pyridyl)methylaminophenyl]-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(93) 2-[2-(3-pyridyl)methylaminophenyl]-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(94) 2-(4-pyridyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(95) N-(2-pyridyl)-[4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one-2-yl]carboxamide,

(96) N-(3-pyridyl)-[4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one-2-yl]carboxamide,

(97) N-(4-pyridyl)-[4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one-2-yl]carboxamide,

(98) 1,3-diphenyl-4-methyl-4,5-dihydro-1,2,4-triazine-6(1H)-one and

(99) 1-phenyl-3-(2-pyridyl)-4-methyl-4,5-dihydro-1,2,4-triazine-6(1H)-one.

REMARKS

The specification has been amended to provide cross-reference to the previously filed International application.

The claims have also been amended to delete the improper multiple dependencies and to place the application into better form prior to examination.

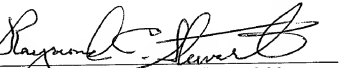
Entry of the above amendments is earnestly solicited. An early and favorable first action on the merits is earnestly solicited.

Attached hereto is a marked-up copy of the changes made to the application by this Amendment.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

BIRCH, STEWART, KOLASCH & BIRCH, LLP

By 

Raymond C. Stewart, # 21,066
P.O. Box 747
Falls Church, VA 22040-0747
(703) 205-8000

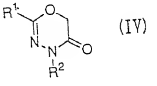
RCS/tf

VERSION WITH MARKINGS TO SHOW CHANGES MADE

The specification has been amended to provide cross-reference to the International Application.

The claims have been amended as follows:

10. (Amended) The heterodiazinon compound according to [claims 7 to 9] claim 7 represented by the following formula (IV):



(IV)

(wherein R^1 and R^2 have the same meanings as defined above), a pharmacologically acceptable salt thereof or hydrates thereof.

11 (Amended) The heterodiazinon compound according to [claims 7 to 10] claim 7, a pharmacologically acceptable salt thereof or hydrates thereof, wherein the aryl group is a group selected from phenyl group, indenyl group, naphthyl group, azulenyl group, heptalenyl group and anthnyl group; the heteroaryl group is a group selected from thienyl group, furyl group, pyranyl group, pyrrolyl group, imidazolyl group, pyrazolyl group, triazolyl group,

tetrazolyl group, isothiazolyl group, thiazolyl group, thiadiazolyl group, isoxazolyl group, pyridyl group, pyrazinyl group, pyrimidyl group, pyridazinyl group, indolizinyl group, isoindolyl group, indolyl group, indazolyl group, isoquinolyl group, quinolyl group, phthalazinyl group, naphthylidinyl group, quinoxalinyl group, quinazolinyl group and cinolynyl group; and the lower cycloalkyl group is a group selected from cyclopropyl group, cyclobutyl group, cyclopentyl group, cyclohexyl group, cycloheptyl group and cycloctyl group.

12. (Amended) The heterodiazinon compound according to [claims 7 to 11] claim 7, which is the compound selected from the following compounds or pharmacologically acceptable salts thereof or hydrates thereof.

(1) 2-(2-Pyridyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(2) 2-(2-Pyrazinyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(3) 2-(1-methyl-2-pyrolyl)-4-phenyl-4H1,3,4-oxadiazine-5(6H)-one,

(4) 2, 4-diphenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(5) 2-(2,3-dimethoxyphenyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(6) 2-(2-pyrrolyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(7) 2-(2-quinolyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(8) 2-(6-methyl-2-pyridyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(9) 2-benzoyloxymethyl-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(10) 2-(2-pyridyl)-4-(2,4-difluorophenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(11) 2-(2-pyridyl)-4-cyclohexyl-4H-1,3,4-oxadiazine-5(6H)-one,

(12) 2-(2-chloro-4-pyridyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(13) 2-(3-methoxy-2-pyridyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(14) 2-(3-hydroxy-2-pyridyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(15) 2-styryl-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(16) 2-[2-(3-pyridyl)vinyl]-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(17) 2-(2-methoxyphenyl)-4-(2-bromophenyl)-4H-1,3,4-oxadiazine-5 (6H)-one,

(18) 2-(4-nitrophenyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(19) 2-(3-nitrophenyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(20) 2-(2-nitrophenyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(21) 2-(4-morpholinyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-

one,

(22) 2-cyclohexyl-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(23) 2-dimethylamino-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(24) 2-dimethylamino-4-phenyl-4H-1,3,4-thiadiazine-5(6H)-one,

(25) 2-(2,6-dimethoxyphenyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(26) 2-(2-methoxyphenyl)-4-(2-fluorophenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(27) 2-phenyl-4-cyclohexyl-4H-1,3,4-oxadiazine-5(6H)-one,

(28) 2-(2-methoxyphenyl)-4-cyclohexyl-4H-1,3,4-oxadiazine-5(6H)-one,

(29) 2-(3-pyridyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(30) 2-phenyl-4-(2-bromophenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(31) 2-(2-thienyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(32) 2-benzyl-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(33) 2-(2-pyridyl)-4-(2-bromophenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(34) 2-(2-pyridyl)-4-(2-fluorophenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(35) 2-(2-pyridyl)-4-(2-methoxyphenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(36) 2-phenyl-4-(2-cyanophenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(37) 2-phenyl-4-(2-nitrophenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(38) 2-phenyl-4-(2-pyridyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(39) 2-phenyl-4-(3-pyridyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(40) 2-phenyl-4-(3-cyano-2-pyridyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(41) 2-phenyl-4-(2-hydroxymethylphenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(42) 2-phenyl-4-(2-cyano-3-pyridyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(43) 2-phenyl-4-(2-thienyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(44) 2-phenyl-4-(3-thienyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(45) 2-phenyl-4-(4-cyanophenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(46) 2-phenyl-4-(3-cyanophenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(47) 2-phenyl-4-(2-cyano-3-thienyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(48) 2-(2-hydroxyphenyl)-4-(2-bromophenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(49) 2-(2-hydroxyphenyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(50) 2-phenyl-4-(2-hydroxyphenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(51) 2-(2-hydroxyphenyl)-4-(2-fluorophenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(52) 2-(2-hydroxyphenyl)-4-(4-fluorophenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(53) 2-(2-hydroxyphenyl)-4-(2,4-difluorophenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(54) 2-[2-(2-dimethylamino)ethoxyphenyl]-4-(2-bromophenyl)-4 H-1,3,4-oxadiazine-5(6H)-one,

(55) 2-[2-(4-pyridyl)methoxyphenyl]-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(56) 2-{2-[2-(4-morpholinyl)ethoxy]phenyl}-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(57) 2-[2-(2-pyridyl)methoxyphenyl]-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(58) 2-[2-(3-pyridyl)methoxyphenyl]-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(59) 2-{2-[2-(1-piperidyl)ethoxy]phenyl}-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(60) 2-{2-[2-(1-pyrrolidinyl)ethoxy]phenyl}-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(61) 2-[2-(2-dimethylaminoethoxy)phenyl]-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(62) 2-[2-(3-dimethylaminopropoxy)phenyl]-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(63) 2-{2-[3-(1-piperidinyl)propoxy]phenyl}-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(64) 2-phenyl-{4-[2-(4-morpholinyl)ethoxy]phenyl}-4H-1,3,4-oxadiazine-5(6H)-one,

(65) 2-phenyl-4-[2-(2-dimethylaminoethoxy)phenyl]-4H-1,3,4-oxadiazine-5(6H)-one,

(66) 2-[2-(2-dimethylaminoethoxy)phenyl]-4-(2-fluorophenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(67) 2-{2-[2-(4-morpholinyl)ethoxy]phenyl}-4-(2-fluorophenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(68) 2-{2-[2-(4-morpholinyl)ethoxy]phenyl}-4-(2-bromophenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(69) 2-{2-[2-(4-morpholinyl)ethoxy]phenyl}-4-cyclohexyl-4H-1,3,4-oxadiazine-5(6H)-one,

(70) 2-{2-[2-(4-morpholinyl)ethoxy]phenyl}-4-(4-fluorophenyl)-4 H-1,3,4-oxadiazine-5(6H)-one,

(71) 2-{2-[2-(4-morpholinyl)ethoxy]phenyl}-4-(2,4-difluorophenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(72) 2-[3-(2-hydroxyethoxy)-2-pyridyl]-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(73) 2-{3-[2-(4-morpholinyl)ethoxy]-2-pyridyl}-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(74) 2-{3-[2-(1-piperidyl)ethoxy]-2-pyridyl}-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(75) 2-{3-[2-(1-pyrrolidinyl)ethoxy]-2-pyridyl}-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(76) 2-{3-[2-(1-methyl-2-pyrrolidinyl)ethoxy]-2-pyridyl}-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(77) 2-[3-(2-dimethylaminoethoxy)-2-pyridyl]-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(78) 2-(3-aminophenyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(79) 2-(2-aminophenyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(80) 2-phenyl-4-(tetrahydro-4H-pyran-4-yl)-4H-1,3,4-oxadiazine-5(6H)-one,

(81) 2-phenyl-4-(1-methyl-4-piperidyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(82) 2-phenyl-4-(3-quinuclidinyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(83) 2-pyridyl-4-(1-benzyl-4-piperidyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(84) 2-phenyl-4-(3-tetrahydrofuranyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(85) 2-phenyl-4-cyclopentyl-4H-1,3,4-oxadiazine-5(6H)-one,

(86) 2-phenyl-4-(1-benzyl-4-piperidyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(87) 2-phenyl-4-[1-(2-pyridyl)ethyl]-4H-1,3,4-oxadiazine-5(6H)-one,

(88) 2-phenyl-4-[1-(3-pyridyl)ethyl]-4H-1,3,4-oxadiazine-5(6H)-one,

(89) 2-phenyl-4-[1-(4-pyridyl)ethyl]-4H-1,3,4-oxadiazine-5(6H)-one,

(90) 2-(3-dimethylaminophenyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(91) 2-(2-dimethylaminophenyl)-4-phenyl-4H-1,3,4-

oxadiazine-5(6H)-one,

(92) 2-[2-(4-pyridyl)methylaminophenyl]-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(93) 2-[2-(3-pyridyl)methylaminophenyl]-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(94) 2-(4-pyridyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(95) N-(2-pyridyl)-[4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one-2-yl]carboxamide,

(96) N-(3-pyridyl)-[4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one-2-yl]carboxamide,

(97) N-(4-pyridyl)-[4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one-2-yl]carboxamide,

(98) 1,3-diphenyl-4-methyl-4,5-dihydro-1,2,4-triazine-6(1H)-one and

(99) 1-phenyl-3-(2-pyridyl)-4-methyl-4,5-dihydro-1,2,4-triazine-6(1H)-one.

Description

Heterodiazinon compound

Field of the Invention

The present invention relates to a clinically highly useful pharmaceutical preparation having non-N-methyl-D-aspartate (non-NMDA) excitatory amino acid receptor antagonistic action, for example 2-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor antagonistic action, which is useful specifically as an agent for preventing, treating and ameliorating nerve degeneration diseases, more specifically 1) acute nerve degeneration after cerebral ischemia and cerebrospinal injuries, 2) chronic nerve degeneration diseases such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis (ALS) or Huntington's chorea, 3) epilepsy, 4) pain, 5) spastic paralysis or 6) demyelinating diseases such as multiple sclerosis (MS), encephalomyelitis, Guillain Barre syndrome, Marchiafava Bignami disease, Devic disease, Balo disease, HIV or HTLV myelopathy, and leukoencephalopathy.

Prior Art

Amino acids such as glutamic acid and aspartic acid are known as excitatory amino acids (hereinafter abbreviated to EAAs) governing excitatory neurotransmission in the central

nervous system. It is reported that excessive release or accumulation of these EAAs in synaptic clefts in nerve cells causes abnormal excitation in the central nervous system, thus leading to nerve degeneration, mental disorders and motor function disorders observed after cerebral ischemia, traumas in the head, cerebrospinal injuries, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, Huntington's chorea, AIDS-related nerve disorder, epilepsy or low-oxygen condition. It is also reported that the abnormal excitation in the central nervous system is related to pain and spasm. Further, it is reported that EAAs are involved in nerve disorders caused by toxins contained in foods. Accordingly, a chemical regulating the abnormal functions of EAAs is considered useful as a therapeutic agent for nerve degeneration and spiritual disorders. Furthermore, it is also considered useful as an analgesic for pain etc. originating in chronic pain, migraine, cancerous pain, diabetic nerve disorders, and as a muscle relaxant (Lipton and Rosenberg, N. Eng. J. Med., 330, 613, 1994, Lees, CNS Drugs, 5, 51, 1996, Turski et al., J. Pharmacol. Exp. Ther., 260, 742, 1992). The action of EAA is demonstrated via a glutamate receptor that is a specific receptor present in presynaptic membrane and postsynaptic membrane. This receptor is classified on the basis of electrophysiological or neurochemical properties into (1) N-methyl-D-aspartic acid (NMDA) receptor, (2) non-NMDA receptor, that is, 2-amino-3-hydroxy-5-methyl-4-isoxazole

propionic acid (AMPA) receptor and kainic acid receptor, and (3) metabolism antagonism type glutamate receptor.

EAAs activate the above glutamate receptor and transmits excitation in the central nervous system. Further, it is reported that nerve disorders occur when excess EAA, NMDA, AMPA or kainic acid acts on nerve cells (Meldrum, B., Brain Res. Reviews, 18, 293, 1993). It is known that a compound having AMPA receptor antagonistic action shows a nerve-protecting action in a model with ischemia. It is reported that a competitive inhibitor, 2,3-dihydroxy-6-nitro-7-sulfamoyl-benzo[f-]quinoxaline (referred to hereinafter as NBQX) is effective in an experimental animal model with cerebral ischemia (Sheardown et al., Science, 247, 571, 1990). Further, a non-competitive inhibitor GYKI 52466 (1-(amino-phenyl)-4-methyl-7,8-methylenedioxy-5 H-2,3-benzoazepine hydrochloride) exerts a nerve-protecting action in a rat model with cerebral ischemia (Le Peillet et al., Brain Research, 571, 115, 1992). These reports suggest that the AMPA inhibitor inhibits nerve degeneration after cerebral ischemia. The compound having AMPA receptor antagonistic action is reported as follows. WO 96/10023 and WO 94/25469 disclose quinoxalinedione compounds having a competitive inhibitory action on AMPA receptors. Further, WO 95/01357, WO 97/43276 and DE 19643037 disclose compounds having non-competitive inhibitory action on AMPA receptors.

Cerebral ischemia is a highly frequent acute degeneration

disease in the central nervous system. This disease is caused by occlusion of vessels for supplying blood to the brain or by systemic circulatory disturbance such as cardiac standstill, and irreversible necrosis of nerve cells in the brain is caused by shortage of blood supplied. As a result, disturbance such as motor disturbance including paralysis in hands and legs, hindrance of sensibility, abnormal behavior, etc. is brought about as sequelae. Therapy for preventing necrosis of brain nerve cells at an acute stage from a few hours to a few days after onset is very important for relieving sequelae. Further, there is an attempt at recovering blood stream at a stage called an ultra-acute stage, but symptomatic treatment against brain edema and general control are merely conducted, and there is no established method effective in many cases.

Traumas in the head and spinal injuries are acute degeneration diseases in cells in the central nervous system, and are often accompanied by cerebral ischemic conditions. These diseases cause paralysis, hindrance of sensibility, abnormal behavior etc. as sequelae. After onset, protection of the cells by early therapy is important, but therapeutic methods conducted so far are symptomatic treatment such as inhibition of edema and surgical removal of damaged sites, which does not necessarily lead to a reduction in the sequelae.

Chronic nerve degeneration diseases such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis and Huntington's chorea occur due to degeneration of nerve cells

in the brain and spinal cord. Detailed causes for these diseases remain unclear, and no therapeutic method is established for inhibiting the degeneration of nerve cells in these diseases.

Epilepsy is a repetitive spasmodic disorder caused by abnormal excitation of cerebral nerve cells and may be accompanied by hindrance of consciousness or hindrance of sensibility. For therapy of epilepsy, administration of an anti-spastic agent is conducted, but there may occur severe hepatic disturbance or side effects such as poor-regeneration anemia, skin mucous membrane eye syndrome etc.

Pain (sharp pain) is a clinical symptom caused by various diseases. For treatment of pain, administration of an antalgic is usually conducted, but there is a certain pain not responding to a conventional antalgic.

Spastic paralysis is a clinical symptom caused by promotion of abnormal muscular tension, to cause motor disturbance. For treatment of spastic paralysis, a muscular relaxant is administered, but side effects such as drowsiness, sense of exhaustion and sedative action occur highly frequently.

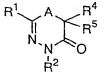
Demyelinating diseases are diseases caused by various causes. These diseases are accompanied by paresthesia, pain, spastic paralysis, micturition disturbance etc. Among these diseases, multiple sclerosis that is a demyelinating disease in the central nervous system is a recurring progressive disease,

and there is no established therapeutic method.

There is no practical therapeutic, ameliorating or preventive agent for acute nerve degeneration diseases after cerebral ischemia and cerebrospinal injuries, chronic nerve degeneration disease, epilepsy, pain, spastic paralysis, and demyelinating disease by use of non-NMDA excitatory amino acid receptor antagonistic action, particularly AMPA receptor antagonistic action, and its development is desired.

Disclosure of the Invention

The present inventors paid attention to compounds having non-NMDA excitatory amino acid receptor antagonistic action, particularly AMPA receptor antagonistic action, and made extensive study. As a result, they succeeded in synthesizing a novel heterodiazinon compound represented by the formula:



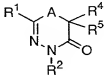
(I)

as well as a pharmacologically acceptable salt thereof. Further, they found that these compounds have an excellent pharmacological action, are excellent in safety and can solve the problem described above, thus completing the present invention. Accordingly, the object of the present invention is to provide a clinically highly useful, novel pharmaceutical preparation having good balance between effects and side effects thereby solving the drawbacks of conventional agents

such as an agent for treatment of acute nerve degeneration diseases after cerebral ischemia and cerebrospinal injuries, an agent for treatment of chronic nerve degeneration disease, anti-epileptic agent, an analgesic, a muscle relaxant, or an agent for treatment of demyelinating disease.

That is, the first aspect of the present invention relates to:

1) a heterodiazinon compound represented by the formula:

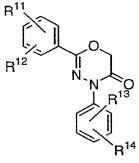


(I)

(wherein A represents oxygen, sulfur or a group represented by the formula >NR^3 (wherein R^3 represents hydrogen atom or a lower alkyl group); R^1 and R^2 are the same as or different from each other and each represents an optionally substituted aryl group, an optionally substituted heteroaryl group, an optionally substituted aralkyl group, an optionally substituted heteroaryl alkyl group, an optionally substituted aryl alkenyl group, an optionally substituted heteroaryl alkenyl group, an optionally substituted piperidyl group, an optionally substituted piperazinyl group, a morpholinyl group, an optionally substituted lower cycloalkyl group, a tetrahydrofuranyl group, a tetrahydropyranyl group, an adamantyl group, an optionally substituted amino group or an optionally substituted amide group; and R^4 and R^5 are the same as or different from each other and each represents hydrogen

atom, hydroxyl group, a halogen atom, nitrile group, nitro group, a lower alkyl group, an aryl group or a heteroaryl group), a pharmacologically acceptable salt thereof or hydrates thereof,

provided that the compounds represented by the following formula (II):



(II)

(wherein R^{11} and R^{12} are the same as or different from each other and each represents hydrogen atom, fluorine, chlorine, bromine, iodine, a C1-C2 fluoroalkyl group, a C1-C2 chloroalkyl group, a C1-C2 bromoalkyl group, a C1-C6 alkyl group, a C3-C6 cycloalkyl group, a C7-C9 aralkyl group, phenyl group, a C1-C6 alkoxy group, a C1-C6 alkylthio group, a C1-C6 alkylsulfinyl group, a C7-C9 aralkoxy group, phenoxy group, phenylthio group, phenylsulfonyl group, an alkali metal carboxylate C2-C5 alkoxycarbonyl group or a group represented by the formula $-N(R^{15})R^{16}$ (wherein R^{15} and R^{16} are the same as or different from each other and each represents hydrogen atom or a C1-C2 alkyl group); and R^{13} and R^{14} are the same as or different from each other and each represents a C_{1-4} alkylsulfonyl group, nitro group, a group represented by the formula $-OCH_nX_{3-n}$ (wherein X represents fluorine, chlorine, bromine or iodine; and n is an integer of 1 to 3) or the same groups as defined above for R^{11}

and R^{12}) are excluded;

2) the heterodiazinon compound according to 1), a pharmacologically acceptable salt thereof or hydrates thereof, wherein R^4 and R^5 are the same as or different from each other and each represents hydrogen atom, hydroxyl group, a C_{1-6} alkyl group or an aryl group;

3) the heterodiazinon compound according to 1), a pharmacologically acceptable salt thereof or hydrates thereof, wherein R^4 is hydrogen atom and R^5 is hydroxyl group, a C_{1-6} alkyl group or an aryl group;

4) the heterodiazinon compound according to 1), a pharmacologically acceptable salt thereof or hydrates thereof, wherein R^4 is hydrogen atom and R^5 is hydroxyl group, methyl group, ethyl group, n-propyl group, i-propyl group or phenyl group;

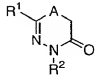
5) the heterodiazinon compound according to 1), a pharmacologically acceptable salt thereof or hydrates thereof, wherein R^4 and R^5 are the same as or different from each other and each represents methyl group, ethyl group, n-propyl group or i-propyl group; and

6) the heterodiazinon compound according to 1), a pharmacologically acceptable salt thereof or hydrates thereof, wherein A is oxygen.

The above heterodiazinon compound (I) wherein R^4 and R^5 are hydrogen atoms is the same as the following heterodiazinon compound (III).

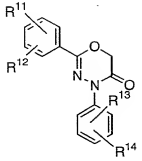
Further, the second aspect of the present invention relates to:

7) a heterodiazinon compound (III) represented by the following formula:



(III)

(wherein A represents oxygen, sulfur or a group represented by the formula $>NR^3$ (wherein R^3 represents hydrogen atom or a lower alkyl group); and R^1 and R^2 are the same as or different from each other and each represents an optionally substituted aryl group, an optionally substituted heteroaryl group, an optionally substituted aralkyl group, an optionally substituted heteroaryl alkyl group, an optionally substituted aryl alkenyl group, an optionally substituted heteroaryl alkenyl group, an optionally substituted piperidyl group, an optionally substituted piperazinyl group, a morpholinyl group, an optionally substituted lower cycloalkyl group, a tetrahydrofuranyl group, a tetrahydropyranyl group, an adamantyl group, an optionally substituted amino group or an optionally substituted amide group), a pharmacologically acceptable salt thereof or hydrates thereof, provided that the heterodiazinon compounds represented by the formula (II):



(II)

(wherein R^{11} and R^{12} are the same as or different from each other and each represents hydrogen atom, fluorine, chlorine, bromine, iodine, a C1-C2 fluoroalkyl group, a C1-C2 chloroalkyl group, a C1-C2 bromoalkyl group, a C1-C6 alkyl group, a C3-C6 cycloalkyl group, a C7-C9 aralkyl group, phenyl group, a C1-C6 alkoxy group, a C1-C6 alkylthio group, a C1-C6 alkylsulfinyl group, a C7-C9 aralkoxy group, phenoxy group, phenylthio group, phenylsulfonyl group, an alkali metal carboxylate C2-C5 alkoxycarbonyl group or a group represented by the formula $-N(R^{15})R^{16}$ (wherein R^{15} and R^{16} are the same as or different from each other and each represents hydrogen atom or a C1-C2 alkyl group); and R^{13} and R^{14} are the same as or different from each other and each represents a C_{1-4} alkylsulfonyl group, nitro group, a group represented by the formula $-OCH_nX_{3-n}$ (wherein X represents fluorine, chlorine, bromine or iodine; and n is an integer of 1 to 3) or the same groups as defined above for R^{11} and R^{12}) are excluded;

8) the heterodiazinon compound according to 7), a pharmacologically acceptable salt thereof or hydrates thereof, wherein R^1 is an optionally substituted aryl group, an optionally substituted heteroaryl group, an optionally

substituted aralkyl group, an optionally substituted heteroaryl alkyl group, an optionally substituted aryl alkenyl group, an optionally substituted heteroaryl alkenyl group, a morpholinyl group, a lower cycloalkyl group, an optionally substituted amino group or an optically substituted amide group; and R^2 is an optionally substituted aryl group, an optionally substituted heteroaryl group, an optionally substituted aralkyl group, an optionally substituted heteroaryl alkyl group, a lower cycloalkyl group, a tetrahydrofuranyl group, a tetrahydropyranyl group, an optionally substituted piperidyl group or an adamantyl group;

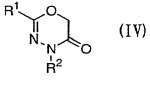
9) the heterodiazinon compound according to 7) or 8), a pharmacologically acceptable salt thereof or hydrates thereof, wherein the substituent groups on R^1 and R^2 are hydrogen atom, halogen atom, hydroxyl group, lower alkyl group, lower alkenyl group, lower alkynyl group, lower alkoxy group, lower thioalkoxy group, hydroxy lower thioalkoxy group, arylthio group, heteroaryl thio group, heteroaryl(hydroxy)alkyl group, halogenated lower alkyl group, hydroxy lower alkyl group, dihydroxy lower alkyl group, halogenated(hydroxy)lower alkyl group, hydroxyalkenyl group, hydroxyalkynyl group, hydroxy lower cycloalkenyl group, lower alkoxy(hydroxy)alkyl group, lower alkoxy(hydroxy)alkoxy group, lower alkoxy alkyl group, lower alkoxy alkoxy group, lower thioalkoxy alkoxy group, lower alkyl sulfonyl alkoxy group, hydroxy lower alkoxy group, dihydroxy lower alkoxy group, hydroxy lower alkyl alkoxy group,

hydroxy imino lower alkyl group, lower cycloalkyl(hydroxy)alkyl group, aralkyl group, hydroxyaralkyl group, cyano group, cyano lower alkyl group, amide group, N-lower alkyl amide group, N-lower cycloalkyl amide group, N,N-di-lower alkyl amide group, N-hydroxy lower alkyl amide group, N-hydroxy lower alkyl-N-lower alkyl amide group, N-aryl amide group, cyclic aminocarbonyl group, carbamoyl group, N-lower alkyl carbamoyl group, N,N-di-lower alkyl carbamoyl group, aminosulfonyl group, cyclic aminosulfonyl group, N-lower alkyl aminosulfonyl group, N-lower cycloalkyl aminosulfonyl group, N,N-di-lower alkyl aminosulfonyl group, N-hydroxy lower alkyl aminosulfonyl group, N-lower alkoxy alkyl aminosulfonyl group, N-halogenated lower alkyl sulfonyl group, pyrrolidinyl sulfonyl group, lower alkyl sulfonyl amino alkyl group, N-lower alkyl aminosulfonyl alkyl group, N,N-di-lower alkyl aminosulfonyl alkyl group, lower acyl group, lower acyl alkyl group, lower cycloalkyl(hydroxy)methyl group, tetrahydropyranyl group, hydroxytetrahydropyranyl group, hydroxy lower alkyl tetrahydropyranyl group, lower acyl amino alkyl group, (thiazole-2-yl) hydroxymethyl group, di(thiazole-2-yl) hydroxymethyl group, lower alkyl sulfonyl group, lower alkoxy alkyl sulfonyl group, hydroxy lower alkyl sulfonyl group, lower alkyl sulfonyl alkyl group, N-lower alkyl amide alkyl group, aryl group, aralkyl group, heteroaryl group, heteroaryl lower alkyl group, heteroaryl lower alkoxy group, heteroaryl sulfonyl group, 4-morpholinyl sulfonyl group, 4-

oxythiomorpholinyl sulfonyl group, 4-dioxythiomorpholinyl sulfonyl group, 4-morpholinyl sulfonyl group, hydroxy lower cycloalkyl group, hydroxy lower cycloalkyloxy group, hydroxy cycloalkenyl group, halogenated hydroxy lower alkyl group, 4-hydroxypiperidyl group, 4-lower alkoxypiperidyl group, ω,ω-lower alkylene dioxyalkyl group, ω,ω-lower alkylene dioxy alkoxy group, lower cycloalkyl hydroxy methyl group, aryloxy group, aryl aminosulfonyl group, amino group, lower alkyl amino group, di-lower alkyl amino group, hydroxy lower alkyl amino group, lower acyl amino group, hydroxy lower acyl amino group, lower alkyl sulfonyl amino group, pyridyl lower alkoxy group, lower alkyl pyridyl alkoxy group, lower alkoxy hydroxy alkoxy group, lower thioalkoxy alkoxy group, lower alkyl sulfonyl alkoxy group, N-lower alkyl carbamoyl group, N,N-di-lower alkyl carbamoyl group, N-hydroxy lower alkyl carbamoyl group, N-hydroxy lower alkyl-N-lower alkyl carbamoyl group, halogenated lower alkoxy group, cyano lower alkoxy group, hydroxy lower cycloalkoxy group, trifluoromethyl group, trifluoromethoxy group, amino lower alkoxy group, N-lower alkyl aminoalkoxy group, N,N-di-lower alkyl aminoalkoxy group, lower acyl alkoxy group, lower acyl aminoalkoxy group, (1,3-dioxolanyl)lower alkyl group, (1,3-dioxolanyl)lower alkoxy group, amide lower alkoxy group, 4-(hydroxyalkyl)tetrahydropyran-4-yl group, 2,3-dihydrobenzofuranyl group, 2-hydroxy-2-alkyl-2,3-dihydrobenzofuranyl group, indanonyl group, hydroxyindanyl group, imidazolyl lower alkoxy group, succimide group or 2-

oxazolidone-3-yl group, optionally substituted benzoyloxy lower alkyl group, optionally substituted amino lower alkyl group, optionally substituted amino lower alkoxy group, optionally substituted aralkyloxy group, optionally substituted heteroaryl alkoxy group, optionally substituted morpholinyl lower alkoxy group, optionally substituted piperidyl lower alkoxy group, optionally substituted piperazinyl lower alkoxy group or optionally substituted pyrrolidinyl lower alkoxy group;

10) the heterodiazinon derivative according to 7) to 9), a pharmacologically acceptable salt thereof or hydrates thereof, which are represented by the following formula:


(IV)

wherein R^1 and R^2 have the same meanings as defined above;

11) the heterodiazinon compound according to 7) to 10), a pharmacologically acceptable salt thereof or hydrates thereof, wherein the aryl group is a group selected from phenyl group, indenyl group, naphthyl group, azulenyl group, heptalenyl group and anthnyl group; the heteroaryl group is a group selected form thienyl group, furyl group, pyranyl group, pyrrolyl group, imidazolyl group, pyrazolyl group, triazolyl group, tetrazolyl group, isothiazolyl group, thiazolyl group, thiadiazolyl group, isoxazolyl group, pyridyl group, pyrazinyl group, pyrimidyl group, pyridazinyl group, indolizinyl group, isoindolyl group,

indolyl group, indazolyl group, isoquinolyl group, quinolyl group, phthalazinyl group, naphthylidinyl group, quinoxalinyl group, quinazolinyl group and cinolynyl group; and the lower cycloalkyl group is a group selected from cyclopropyl group, cyclobutyl group, cyclopentyl group, cyclohexyl group, cycloheptyl group and cycloctyl group; and

12) the heterodiazinon compound according to 7) to 11), which is a compound selected from the following compounds or pharmacologically acceptable salts thereof or hydrates thereof.

(1) 2-(2-Pyridyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(2) 2-(2-pyrazinyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(3) 2-(1-methyl-2-pyrolyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(4) 2,4-diphenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(5) 2-(2,3-dimethoxyphenyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(6) 2-(2-pyrrolyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(7) 2-(2-quinolyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(8) 2-(6-methyl-2-pyridyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(9) 2-benzoyloxymethyl-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(10) 2-(2-pyridyl)-4-(2,4-difluorophenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(11) 2-(2-pyridyl)-4-cyclohexyl-4H-1,3,4-oxadiazine-5(6H)-

one,

(12) 2-(2-chloro-4-pyridyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(13) 2-(3-methoxy-2-pyridyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(14) 2-(3-hydroxy-2-pyridyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(15) 2-styryl-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(16) 2-[2-(3-pyridyl)vinyl]-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(17) 2-(2-methoxyphenyl)-4-(2-bromophenyl)-4H-1,3,4-oxadiazine-5 (6H)-one,

(18) 2-(4-nitrophenyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(19) 2-(3-nitrophenyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(20) 2-(2-nitrophenyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(21) 2-(4-morpholinyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(22) 2-cyclohexyl-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(23) 2-dimethylamino-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(24) 2-dimethylamino-4-phenyl-4H-1,3,4-thiadiazine-5(6H)-one,

(25) 2-(2,6-dimethoxyphenyl)-4-phenyl-4H-1,3,4-oxadiazine-

5(6H)-one,

(26) 2-(2-methoxyphenyl)-4-(2-fluorophenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(27) 2-phenyl-4-cyclohexyl-4H-1,3,4-oxadiazine-5(6H)-one,

(28) 2-(2-methoxyphenyl)-4-cyclohexyl-4H-1,3,4-oxadiazine-5(6H)-one,

(29) 2-(3-pyridyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(30) 2-phenyl-4-(2-bromophenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(31) 2-(2-thienyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(32) 2-benzyl-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(33) 2-(2-pyridyl)-4-(2-bromophenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(34) 2-(2-pyridyl)-4-(2-fluorophenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(35) 2-(2-pyridyl)-4-(2-methoxyphenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(36) 2-phenyl-4-(2-cyanophenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(37) 2-phenyl-4-(2-nitrophenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(38) 2-phenyl-4-(2-pyridyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(39) 2-phenyl-4-(3-pyridyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(40) 2-phenyl-4-(3-cyano-2-pyridyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(41) 2-phenyl-4-(2-hydroxymethylphenyl)-4H-1,3,4-

oxadiazine-5(6H)-one,

(42) 2-phenyl-4-(2-cyano-3-pyridyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(43) 2-phenyl-4-(2-thienyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(44) 2-phenyl-4-(3-thienyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(45) 2-phenyl-4-(4-cyanophenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(46) 2-phenyl-4-(3-cyanophenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(47) 2-phenyl-4-(2-cyano-3-thienyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(48) 2-(2-hydroxyphenyl)-4-(2-bromophenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(49) 2-(2-hydroxyphenyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(50) 2-phenyl-4-(2-hydroxyphenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(51) 2-(2-hydroxyphenyl)-4-(2-fluorophenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(52) 2-(2-hydroxyphenyl)-4-(4-fluorophenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(53) 2-(2-hydroxyphenyl)-4-(2,4-difluorophenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(54) 2-[2-(2-dimethylamino)ethoxyphenyl]-4-(2-bromophenyl)-4 H-1,3,4-oxadiazine-5(6H)-one,

(55) 2-[2-(4-pyridyl)methoxyphenyl]-4-phenyl-4H-1,3,4-

oxadiazine-5(6H)-one,

(56) 2-{2-[2-(4-morpholinyl)ethoxy]phenyl}-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(57) 2-[2-(2-pyridyl)methoxyphenyl]-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(58) 2-[2-(3-pyridyl)methoxyphenyl]-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(59) 2-{2-[2-(1-piperidyl)ethoxy]phenyl}-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(60) 2-{2-[2-(1-pyrrolidinyl)ethoxy]phenyl}-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(61) 2-[2-(2-dimethylaminoethoxy)phenyl]-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(62) 2-[2-(3-dimethylaminopropoxy)phenyl]-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(63) 2-{2-[3-(1-piperidinyl)propoxy]phenyl}-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(64) 2-phenyl-{4-[2-(4-morpholinyl)ethoxy]phenyl}-4H-1,3,4-oxadiazine-5(6H)-one,

(65) 2-phenyl-4-[2-(2-dimethylaminoethoxy)phenyl]-4H-1,3,4-oxadiazine-5(6H)-one,

(66) 2-[2-(2-dimethylaminoethoxy)phenyl]-4-(2-fluorophenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(67) 2-{2-[2-(4-morpholinyl)ethoxy]phenyl}-4-(2-fluorophenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(68) 2-{2-[2-(4-morpholinyl)ethoxy]phenyl}-4-(2-

bromophenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(69) 2-{2-[2-(4-morpholinyl)ethoxy]phenyl}-4-cyclohexyl-4H-1,3,4-oxadiazine-5(6H)-one,

(70) 2-{2-[2-(4-morpholinyl)ethoxy]phenyl}-4-(4-fluorophenyl)-4 H-1,3,4-oxadiazine-5(6H)-one,

(71) 2-{2-[2-(4-morpholinyl)ethoxy]phenyl}-4-(2,4-difluorophenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(72) 2-[3-(2-hydroxyethoxy)-2-pyridyl]-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(73) 2-{3-[2-(4-morpholinyl)ethoxy]-2-pyridyl}-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(74) 2-{3-[2-(1-piperidyl)ethoxy]-2-pyridyl}-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(75) 2-{3-[2-(1-pyrrolidinyl)ethoxy]-2-pyridyl}-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(76) 2-{3-[2-(1-methyl-2-pyrrolidinyl)ethoxy]-2-pyridyl}-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(77) 2-[3-(2-dimethylaminoethoxy)-2-pyridyl]-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(78) 2-(3-aminophenyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(79) 2-(2-aminophenyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(80) 2-phenyl-4-(tetrahydro-4H-pyran-4-yl)-4H-1,3,4-oxadiazine-5(6H)-one,

(81) 2-phenyl-4-(1-methyl-4-piperidyl)-4H-1,3,4-oxadiazine-

5(6H)-one,

(82) 2-phenyl-4-(3-quinuclidinyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(83) 2-pyridyl-4-(1-benzyl-4-piperidyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(84) 2-phenyl-4-(3-tetrahydrofuranyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(85) 2-phenyl-4-cyclopentyl-4H-1,3,4-oxadiazine-5(6H)-one,

(86) 2-phenyl-4-(1-benzyl-4-piperidyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(87) 2-phenyl-4-[1-(2-pyridyl)ethyl]-4H-1,3,4-oxadiazine-5(6H)-one,

(88) 2-phenyl-4-[1-(3-pyridyl)ethyl]-4H-1,3,4-oxadiazine-5(6H)-one,

(89) 2-phenyl-4-[1-(4-pyridyl)ethyl]-4H-1,3,4-oxadiazine-5(6H)-one,

(90) 2-(3-dimethylaminophenyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(91) 2-(2-dimethylaminophenyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(92) 2-[2-(4-pyridyl)methylaminophenyl]-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(93) 2-[2-(3-pyridyl)methylaminophenyl]-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(94) 2-(4-pyridyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(95) N-(2-pyridyl)-[4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one-

2-yl]carboxamide,

(96) N-(3-pyridyl)-[4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one-2-yl]carboxamide,

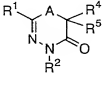
(97) N-(4-pyridyl)-[4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one-2-yl]carboxamide,

(98) 1,3-diphenyl-4-methyl-4,5-dihydro-1,2,4-triazine-6(1H)-one and

(99) 1-phenyl-3-(2-pyridyl)-4-methyl-4,5-dihydro-1,2,4-triazine-6(1H)-one.

Further, the third aspect of the present invention relates to:

13) a pharmaceutical preparation comprising a heterodiazinon compound represented by the formula:

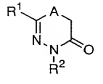


(I)

(wherein A represents oxygen, sulfur or a group represented by the formula $>NR^3$ (wherein R^3 represents hydrogen atom or a lower alkyl group); R^1 and R^2 are the same as or different from each other and each represents an optionally substituted aryl group, an optionally substituted heteroaryl group, an optionally substituted aralkyl group, an optionally substituted heteroaryl alkyl group, an optionally substituted aryl alkenyl group, an optionally substituted heteroaryl alkenyl group, an optionally substituted piperidyl group, an optionally substituted piperazinyl group, a morpholinyl group, an

optionally substituted lower cycloalkyl group, a tetrahydrofuranyl group, a tetrahydropyranyl group, an adamantyl group, an optionally substituted amino group or an optionally substituted amide group; and R^4 and R^5 are the same as or different from each other and each represents hydrogen atom, hydroxyl group, a halogen atom, nitrile group, nitro group, a lower alkyl group, an aryl group or a heteroaryl group), a pharmaceutically acceptable salt thereof or hydrates thereof;

14) a pharmaceutical preparation comprising a heterodiazinon compound represented by the following formula:



(V)

(wherein A represents oxygen, sulfur or a group represented by the formula $>NR^3$ (wherein R^3 represents hydrogen atom or a lower alkyl group); and R^1 and R^2 are the same as or different from each other and each represents an optionally substituted aryl group, an optionally substituted heteroaryl group, an optionally substituted aralkyl group, an optionally substituted heteroaryl alkyl group, an optionally substituted aryl alkenyl group, an optionally substituted heteroaryl alkenyl group, an optionally substituted piperidyl group, an optionally substituted piperazinyl group, a morpholinyl group, an optionally substituted lower cycloalkyl group, a tetrahydrofuranyl group, a tetrahydropyranyl group, an adamantyl group, an optionally substituted amino group or an

optionally substituted amide group), or a pharmaceutically acceptable salt thereof or hydrates thereof;

15) the pharmaceutical preparation according to 13) or 14) for use as an agent for preventing, treating and ameliorating diseases against which non-N-methyl-D-aspartate excitatory amino acid receptor antagonistic action is effective;

16) the pharmaceutical preparation according to 13) or 14) for use as an agent for preventing, treating and ameliorating diseases against which 2-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor antagonistic action is effective;

17) the pharmaceutical preparation according to 13) or 14) for use as an agent for preventing, treating and ameliorating nerve degeneration diseases;

18) the pharmaceutical preparation according to 13) or 14) for use as an agent for preventing, treating and ameliorating demyelinating nerve diseases;

19) the pharmaceutical preparation according to 13) or 14) for use as an agent for preventing, treating and ameliorating acute nerve degeneration after cerebral ischemia, traumas in the head and spinal injuries, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, Huntington's chorea, epilepsy, pain, multiple sclerosis, encephalomyelitis, Guillain Barre syndrome, Marchiafava Bignami disease, Devic disease, Balo disease, HIV or HTLV

myelopathy or leukoencephalopathy; and

20) the heterodiazinon compound of the present invention which as a compound having non-NMDA excitatory amino acid receptor antagonistic action, particularly AMPA receptor antagonistic action, is used as an agent for preventing, treating and ameliorating nerve degeneration diseases, specifically 1) disturbance such as motor disturbance, hindrance of sensibility and abnormal behavior, caused by disturbance after cerebral ischemia and acute nerve degeneration after cerebrospinal injuries; 2) chronic nerve degeneration diseases such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis and Huntington's chorea; 3) epilepsy; 4) chronic pain, migraine, cancerous pain, and pain originating in diabetic nerve disturbance; 5) spastic paralysis or 6) demyelinating diseases such as multiple sclerosis, encephalomyelitis, Guillain Barre syndrome, Marchiafava Bignami disease, Devic disease, Balo disease, REFSAME disease, TANGIEL disease, DEJERIN-SOTAS disease, HIV or HTLV myelopathy, and leukoencephalopathy.

That is, the present invention relates to a method of preventing, treating and ameliorating diseases against which non-N-methyl-D-aspartate excitatory amino acid receptor antagonistic action is effective; a method of preventing, treating and ameliorating diseases against which 2-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor antagonistic action is effective; a method of preventing,

treating and ameliorating nerve degeneration diseases; and a method of preventing, treating and ameliorating acute nerve degeneration after cerebral ischemia, traumas in the head and spinal injuries, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, Huntington's chorea, epilepsy, pain, multiple sclerosis, encephalomyelitis, Guillain Barre syndrome, Marchiafava Bignami disease, Devic disease, Balo disease, HIV or HTLV myelopathy, or leukoencephalopathy, which comprises administering a pharmacologically effective amount of the pharmaceutical preparation to a patient. Further, it relates to use thereof for producing the above-mentioned pharmaceutical preparation and a pharmaceutical composition comprising it.

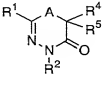
Further, the present invention provides use of the compound represented by the formula (II) above, a pharmacologically acceptable salt thereof or hydrates thereof as a pharmaceutical preparation, and the details are the same as of Compound (I). That is, the present invention provides a pharmaceutical preparation comprising Compound (II) etc., a therapeutic method which comprising administrating the compound, and use thereof for producing a pharmaceutical preparation.

Hereinafter, the meanings of symbols, terms etc. used in the present specification are described, and the present invention is described in detail.

In the specification, the structural formulae of the

compounds may, for convenience' sake, indicate a certain isomer, but the present invention encompasses every possible isomer such as geometric isomer, optical isomer based on asymmetric carbon, stereoisomer and tautomer, which can occur in the structures of the compounds, as well as mixtures of such isomers. Accordingly, the compounds of the present specification are not limited by the formulae shown for convenience' sake, and may be a certain isomer or a mixture thereof. Further, the compounds of the present invention encompass those in any crystalline polymorphism without limitation, and they may be crystals in single crystal form or a mixture thereof, or anhydrates thereof or hydrates thereof.

The heterodiazinon compound of the present invention, a pharmacologically acceptable salt thereof or hydrates thereof are represented by the following formula:

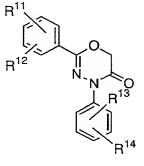


(I)

wherein A represents oxygen, sulfur or a group represented by the formula $>NR^3$ (wherein R^3 represents hydrogen atom or a lower alkyl group); R^1 and R^2 are the same as or different from each other and each represents an optionally substituted aryl group, an optionally substituted heteroaryl group, an optionally substituted aralkyl group, an optionally substituted heteroaryl alkyl group, an optionally substituted aryl alkenyl group, an optionally substituted heteroaryl alkenyl group, an

optionally substituted piperidyl group, an optionally substituted piperazinyl group, a morpholinyl group, an optionally substituted lower cycloalkyl group, a tetrahydrofuranyl group, a tetrahydropyranyl group, an adamantyl group, an optionally substituted amino group or an optionally substituted amide group; and R^4 and R^5 are the same as or different from each other and each represents hydrogen atom, hydroxyl group, a halogen atom, nitrile group, nitro group, a lower alkyl group, an aryl group or a heteroaryl group,

provided that the compound disclosed in US-4,670,555 (US-4,782,066), represented by the following formula (II) is excluded.



(II)

In the formula, R^{11} and R^{12} are the same as or different from each other and each represents hydrogen atom, fluorine, chlorine, bromine, iodine, a C1-C2 fluoroalkyl group, a C1-C2 chloroalkyl group, a C1-C2 bromoalkyl group, a C1-C6 alkyl group, a C3-C6 cycloalkyl group, a C7-C9 aralkyl group, phenyl group, a C1-C6 alkoxy group, a C1-C6 alkylthio group, a C1-C6 alkylsulfinyl group, a C7-C9 aralkoxy group, phenoxy group, phenylthio group, phenylsulfonyl group, an alkali metal carboxylate C2-C5 alkoxycarbonyl group or a group represented

by the formula $-N(R^{15})R^{16}$ (wherein R^{15} and R^{16} are the same as or different from each other and each represents hydrogen atom or a C1-C2 alkyl group); and R^{13} and R^{14} are the same as or different from each other and each represents a C_{1-4} alkylsulfonyl group, nitro group, a group represented by the formula $-OCH_nX_{3-n}$ (wherein X represents fluorine, chlorine, bromine or iodine; and n is an integer of 1 to 3) or the same groups as defined above for R^{11} and R^{12}.

The compounds disclosed in the above-mentioned US-4,670,555 (US-4,782,066) are concerned with a nematocidal agent or a miticidal agent, and are completely different in chemical structure and pharmacological action from the heterodiazinon compounds of the present invention.

In the definition of the present invention, the lower alkyl group refers to C_{1-6} alkyl groups, for example straight-chain or branched alkyl groups such as methyl group, ethyl group, n-propyl group, i-propyl group, n-butyl group, i-butyl group, t-butyl group, n-pentyl group, i-pentyl group, neopentyl group, hexyl group, 1-methyl propyl group, 1-methyl butyl group and 2-methyl butyl group.

The lower alkoxy group refers to a group having the above lower alkyl group bound to oxygen, and include e.g. straight-chain or branched alkoxy groups such as methoxy group, ethoxy group, n-propoxy group, i-propoxy group, n-butoxy group, i-butoxy group, t-butoxy group, pentyloxy group and hexyloxy group.

The halogen atom refers specifically to fluorine, chlorine, bromine or iodine.

The aryl group refers to a hydrocarbon group that has formed an aromatic ring, and includes e.g. a phenyl group, indenyl group, naphthyl group, azulenyl group, heptalenyl group, anthnyl group etc., which may further be substituted. Among these groups, a phenyl group is more preferable.

The heteroaryl group refers to a group that has been formed from carbon atoms and hydrogen atoms together with one or more nitrogen atoms, oxygen atoms or sulfur atoms, and examples thereof include thienyl group, furyl group, pyranyl group, pyrrolyl group, imidazolyl group, pyrazolyl group, triazolyl group, tetrazolyl group, isothiazolyl group, thiazolyl group, thiadiazolyl group, isoxazolyl group, pyridyl group, pyrazinyl group, pyrimidyl group, pyridazinyl group, indolizinyl group, isoindolyl group, indolyl group, indazolyl group, isoquinolyl group, quinolyl group, phthalazinyl group, naphthylidinyl group, quinoxalinyl group, quinazolinyl group and cinolynyl group, and these groups may be further substituted. Among these groups, a pyridyl group, pyrazinyl group, pyrrolyl group, quinolyl group and thienyl group are more preferable.

The lower cycloalkyl group refers to C_{3-8} cyclic hydrocarbon groups such as cyclopropyl group, cyclobutyl group, cyclopentyl group, cyclohexyl group, cycloheptyl group and cycloctyl group. Among these groups, a cyclohexyl group is more preferable.

The optionally substituted amino group or the optionally substituted amide group refers to groups of the formula $-NH_2$ or $-CONH_2$, or to groups of the formula wherein one or two hydrogen atoms on the nitrogen atom have been replaced. Although the type of the substituent group is not limited, a lower alkyl group can be specifically mentioned.

The substituent groups on R^1 and R^2 include, but are not limited to, hydrogen atom, halogen atom, hydroxyl group, lower alkyl group, lower alkenyl group, lower alkynyl group, lower alkoxy group, lower thioalkoxy group, hydroxy lower thioalkoxy group, arylthio group, heteroaryl thio group, heteroaryl(hydroxy)alkyl group, halogenated lower alkyl group, hydroxy lower alkyl group, dihydroxy lower alkyl group, halogenated(hydroxy)lower alkyl group, hydroxyalkenyl group, hydroxyalkynyl group, hydroxy lower cycloalkenyl group, lower alkoxy(hydroxy)alkyl group, lower alkoxy(hydroxy)alkoxy group, lower alkoxy alkyl group, lower alkoxy alkoxy group, lower thioalkoxy alkoxy group, lower alkyl sulfonyl alkoxy group, hydroxy lower alkoxy group, dihydroxy lower alkoxy group, hydroxy lower alkyl alkoxy group, hydroxy imino lower alkyl group, lower cycloalkyl(hydroxy)alkyl group, aralkyl group, hydroxyaralkyl group, cyano group, cyano lower alkyl group, amide group, N-lower alkyl amide group, N-lower cycloalkyl amide group, N,N-di-lower alkyl amide group, N-hydroxy lower alkyl amide group, N-hydroxy lower alkyl-N-lower alkyl amide group, N-aryl amide group, cyclic aminocarbonyl group,

carbamoyl group, N-lower alkyl carbamoyl group, N,N-di-lower alkyl carbamoyl group, aminosulfonyl group, cyclic aminosulfonyl group, N-lower alkyl aminosulfonyl group, N-lower cycloalkyl aminosulfonyl group, N,N-di-lower alkyl aminosulfonyl group, N-hydroxy lower alkyl aminosulfonyl group, N-lower alkoxy alkyl aminosulfonyl group, N-halogenated lower alkyl sulfonyl group, pyrrolidinyl sulfonyl group, lower alkyl sulfonyl amino alkyl group, N-lower alkyl aminosulfonyl alkyl group, N,N-di-lower alkyl aminosulfonyl alkyl group, lower acyl group, lower acyl alkyl group, lower cycloalkyl(hydroxy)methyl group, tetrahydropyranyl group, hydroxytetrahydropyranyl group, hydroxy lower alkyl tetrahydropyranyl group, lower acyl amino alkyl group, (thiazole-2-yl)hydroxymethyl group, di(thiazole-2-yl)hydroxymethyl group, lower alkyl sulfonyl group, lower alkoxy alkyl sulfonyl group, hydroxy lower alkyl sulfonyl group, lower alkyl sulfonyl alkyl group, N-lower alkyl amide alkyl group, aryl group, aralkyl group, heteroaryl group, heteroaryl lower alkyl group, heteroaryl lower alkoxy group, heteroaryl sulfonyl group, 4-morpholinyl sulfonyl group, 4-oxythiomorpholinyl sulfonyl group, 4-dioxythiomorpholinyl sulfonyl group, 4-morpholinyl sulfonyl group, hydroxy lower cycloalkyl group, hydroxy lower cycloalkyloxy group, hydroxy cycloalkenyl group, halogenated hydroxy lower alkyl group, 4-hydroxypiperidyl group, 4-lower alkoxypiperidyl group, ω,ω-lower alkylene dioxyalkyl group, ω,ω-lower alkylene dioxy alkoxy group, lower cycloalkyl hydroxy methyl group, aryloxy

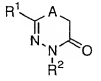
group, aryl aminosulfonyl group, amino group, lower alkyl amino group, di-lower alkyl amino group, hydroxy lower alkyl amino group, lower acyl amino group, hydroxy lower acyl amino group, lower alkyl sulfonyl amino group, pyridyl lower alkoxy group, lower alkyl pyridyl alkoxy group, lower alkoxy hydroxy alkoxy group, lower thioalkoxy alkoxy group, lower alkyl sulfonyl alkoxy group, N-lower alkyl carbamoyl group, N,N-di-lower alkyl carbamoyl group, N-hydroxy lower alkyl carbamoyl group, N-hydroxy lower alkyl-N-lower alkyl carbamoyl group, halogenated lower alkoxy group, cyano lower alkoxy group, hydroxy lower cycloalkoxy group, trifluoromethyl group, trifluoromethoxy group, amino lower alkoxy group, N-lower alkyl aminoalkoxy group, N,N-di-lower alkyl aminoalkoxy group, lower acyl alkoxy group, lower acyl aminoalkoxy group, (1,3-dioxolanyl) lower alkyl group, (1,3-dioxolanyl) lower alkoxy group, amide lower alkoxy group, 4-(hydroxy alkyl) tetrahydropyran-4-yl group, 2,3-dihydrobenzofuranyl group, 2-hydroxy-2-alkyl-2,3-dihydrobenzofuranyl group, indanonyl group, hydroxyindanyl group, imidazolyl lower alkoxy group, succimide group or 2-oxazolidone-3-yl group, optionally substituted benzoyloxy lower alkyl group, optionally substituted amino lower alkyl group, optionally substituted amino lower alkoxy group, optionally substituted aralkyloxy group, optionally substituted heteroaryl alkoxy group, optionally substituted morpholinyl lower alkoxy group, optionally substituted piperidyl lower alkoxy group, optionally substituted

piperazinyl lower alkoxy group and optionally substituted pyrrolidinyl lower alkoxy group.

Among those enumerated above, more preferable groups include a hydroxyl group, halogen atom, optionally substituted amino group, lower alkyl group, lower alkoxy group, nitro group, cyano group, hydroxy lower alkyl group, optionally substituted benzoyloxy lower alkyl group, optionally substituted amino lower alkyl group, optionally substituted amino lower alkoxy group, optionally substituted aralkyloxy group, optionally substituted heteroaryl alkoxy group, optionally substituted morpholinyl lower alkoxy group, optionally substituted piperidyl lower alkoxy group, optionally substituted piperazinyl lower alkoxy group, optionally substituted pyrrolidinyl lower alkoxy group, and hydroxy lower alkoxy group.

In the formula (I) above, R^4 and R^5 are the same as or different from each other and each preferably represents hydrogen atom, hydroxyl group, a C_{1-6} alkyl group or an aryl group; more preferably R^4 represents hydrogen atom while R^5 represents hydrogen atom, hydroxyl group, a C_{1-6} alkyl group or an aryl group; further preferably R^4 represents hydrogen atom while R^5 represents hydrogen atom, hydroxyl group, methyl group, ethyl group, n-propyl group, i-propyl group or phenyl group; and most preferably R^4 and R^5 are the same as or different from each other and each represents hydrogen atom, methyl group, ethyl group, n-propyl group or i-propyl group.

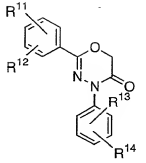
In the case of the above formula (I) wherein R^4 and R^5 are hydrogen atoms, the heterodiazinon compounds (III) are represented by the following formula:



(III)

wherein A represents oxygen, sulfur or a group represented by the formula $>NR^3$ (wherein R^3 represents hydrogen atom or a lower alkyl group); and R^1 and R^2 are the same as or different from each other and each represents an optionally substituted aryl group, an optionally substituted heteroaryl group, an optionally substituted aralkyl group, an optionally substituted heteroaryl alkyl group, an optionally substituted aryl alkenyl group, an optionally substituted heteroaryl alkenyl group, an optionally substituted piperidyl group, an optionally substituted piperazinyl group, a morpholinyl group, an optionally substituted lower cycloalkyl group, a tetrahydrofuranyl group, a tetrahydropyranyl group, an adamantyl group, an optionally substituted amino group or an optionally substituted amide group.

However, the compounds disclosed in US-4,670,555 (US-4,782,066), represented by the following formula (II):



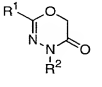
(II)

(wherein R^{11} and R^{12} are the same as or different from each other and each represents hydrogen atom, fluorine, chlorine, bromine, iodine, a C1-C2 fluoroalkyl group, a C1-C2 chloroalkyl group, a C1-C2 bromoalkyl group, a C1-C6 alkyl group, a C3-C6 cycloalkyl group, a C7-C9 aralkyl group, phenyl group, a C1-C6 alkoxy group, a C1-C6 alkylthio group, a C1-C6 alkylsulfinyl group, a C7-C9 aralkoxy group, phenoxy group, phenylthio group, phenylsulfonyl group, an alkali metal carboxylate C2-C5 alkoxycarbonyl group or a group represented by the formula $-N(R^{15})R^{16}$ (wherein R^{15} and R^{16} are the same as or different from each other and each represents hydrogen atom or a C1-C2 alkyl group); and R^{13} and R^{14} are the same as or different from each other and each represents a C_{1-4} alkylsulfonyl group, nitro group, a group represented by the formula $-OCH_nX_{3-n}$ (wherein X represents fluorine, chlorine, bromine or iodine; and n is an integer of 1 to 3) or the same groups as defined above for R^{11} and R^{12}) are excluded.

In the above definition, the "lower alkyl group", "lower alkoxy group", "halogen atom", "aryl group", "heteroaryl group", "lower cycloalkyl group", "optionally substituted amino group", "optionally substituted amide group" and "substituent groups

on R^1 and/or $R^{2''}$ have the same meanings as defined above. Preferable among those enumerated above are hydroxyl group, halogen atom, optionally substituted amino group, lower alkyl group, lower alkoxy group, nitro group, cyano group, hydroxy lower alkyl group, optionally substituted benzoyloxy lower alkyl group, optionally substituted amino lower alkyl group, optionally substituted amino lower alkoxy group, optionally substituted aralkyloxy group, optionally substituted heteroaryl alkoxy group, optionally substituted morpholinyl lower alkoxy group, optionally substituted piperidyl lower alkoxy group, optionally substituted piperazinyl lower alkoxy group, optionally substituted pyrrolidinyl lower alkoxy group, and hydroxy lower alkoxy group.

The heterodiazinon compounds (III) according to the present invention include oxadiazinon compound, thiadiazine compounds and triazine compounds depending on a difference in A in the formula, preferably the oxadiazinon compounds represented by formula (IV):


(IV)

(wherein R^1 and R^2 have the same meanings as defined above), and the following compounds, a pharmacologically acceptable salt thereof or hydrates thereof. It goes without saying that the following compounds are not intended to limit the present invention.

(1) 2-(2-Pyridyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(2) 2-(2-pyrazinyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(3) 2-(1-methyl-2-pyrolyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(4) 2,4-diphenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(5) 2-(2,3-dimethoxyphenyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(6) 2-(2-pyrrolyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(7) 2-(2-quinolyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(8) 2-(6-methyl-2-pyridyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(9) 2-benzoyloxymethyl-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(10) 2-(2-pyridyl)-4-(2,4-difluorophenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(11) 2-(2-pyridyl)-4-cyclohexyl-4H-1,3,4-oxadiazine-5(6H)-one,

(12) 2-(2-chloro-4-pyridyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(13) 2-(3-methoxy-2-pyridyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(14) 2-(3-hydroxy-2-pyridyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(15) 2-styryl-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(16) 2-[2-(3-pyridyl)vinyl]-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(17) 2-(2-methoxyphenyl)-4-(2-bromophenyl)-4H-1,3,4-oxadiazine-5 (6H)-one,

(18) 2-(4-nitrophenyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(19) 2-(3-nitrophenyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(20) 2-(2-nitrophenyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(21) 2-(4-morpholinyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(22) 2-cyclohexyl-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(23) 2-dimethylamino-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(24) 2-dimethylamino-4-phenyl-4H-1,3,4-thiadiazine-5(6H)-one,

(25) 2-(2,6-dimethoxyphenyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(26) 2-(2-methoxyphenyl)-4-(2-fluorophenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(27) 2-phenyl-4-cyclohexyl-4H-1,3,4-oxadiazine-5(6H)-one,

(28) 2-(2-methoxyphenyl)-4-cyclohexyl-4H-1,3,4-oxadiazine-5(6H)-one,

(29) 2-(3-pyridyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(30) 2-phenyl-4-(2-bromophenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(31) 2-(2-thienyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(32) 2-benzyl-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(33) 2-(2-pyridyl)-4-(2-bromophenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(34) 2-(2-pyridyl)-4-(2-fluorophenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(35) 2-(2-pyridyl)-4-(2-methoxyphenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(36) 2-phenyl-4-(2-cyanophenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(37) 2-phenyl-4-(2-nitrophenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(38) 2-phenyl-4-(2-pyridyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(39) 2-phenyl-4-(3-pyridyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(40) 2-phenyl-4-(3-cyano-2-pyridyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(41) 2-phenyl-4-(2-hydroxymethylphenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(42) 2-phenyl-4-(2-cyano-3-pyridyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(43) 2-phenyl-4-(2-thienyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(44) 2-phenyl-4-(3-thienyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(45) 2-phenyl-4-(4-cyanophenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(46) 2-phenyl-4-(3-cyanophenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(47) 2-phenyl-4-(2-cyano-3-thienyl)-4H-1,3,4-oxadiazine-

5(6H)-one,

(48) 2-(2-hydroxyphenyl)-4-(2-bromophenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(49) 2-(2-hydroxyphenyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(50) 2-phenyl-4-(2-hydroxyphenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(51) 2-(2-hydroxyphenyl)-4-(2-fluorophenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(52) 2-(2-hydroxyphenyl)-4-(4-fluorophenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(53) 2-(2-hydroxyphenyl)-4-(2,4-difluorophenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(54) 2-[2-(2-dimethylamino)ethoxyphenyl]-4-(2-bromophenyl)-4 H-1,3,4-oxadiazine-5(6H)-one,

(55) 2-[2-(4-pyridyl)methoxyphenyl]-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(56) 2-{2-[2-(4-morpholinyl)ethoxy]phenyl}-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(57) 2-[2-(2-pyridyl)methoxyphenyl]-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(58) 2-[2-(3-pyridyl)methoxyphenyl]-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(59) 2-{2-[2-(1-piperidyl)ethoxy]phenyl}-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(60) 2-{2-[2-(1-pyrrolidinyl)ethoxy]phenyl}-4-phenyl-4H-

1,3,4-oxadiazine-5(6H)-one,

(61) 2-[2-(2-dimethylaminoethoxy)phenyl]-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(62) 2-[2-(3-dimethylaminopropoxy)phenyl]-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(63) 2-{2-[3-(1-piperidinyl)propoxy]phenyl}-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(64) 2-phenyl-{4-[2-(4-morpholinyl)ethoxy]phenyl}-4H-1,3,4-oxadiazine-5(6H)-one,

(65) 2-phenyl-4-[2-(2-dimethylaminoethoxy)phenyl]-4H-1,3,4-oxadiazine-5(6H)-one,

(66) 2-[2-(2-dimethylaminoethoxy)phenyl]-4-(2-fluorophenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(67) 2-{2-[2-(4-morpholinyl)ethoxy]phenyl}-4-(2-fluorophenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(68) 2-{2-[2-(4-morpholinyl)ethoxy]phenyl}-4-(2-bromophenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(69) 2-{2-[2-(4-morpholinyl)ethoxy]phenyl}-4-cyclohexyl-4H-1,3,4-oxadiazine-5(6H)-one,

(70) 2-{2-[2-(4-morpholinyl)ethoxy]phenyl}-4-(4-fluorophenyl)-4 H-1,3,4-oxadiazine-5(6H)-one,

(71) 2-{2-[2-(4-morpholinyl)ethoxy]phenyl}-4-(2,4-difluorophenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(72) 2-[3-(2-hydroxyethoxy)-2-pyridyl]-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(73) 2-{3-[2-(4-morpholinyl)ethoxy]-2-pyridyl}-4-phenyl-4H-

1,3,4-oxadiazine-5(6H)-one,

(74) 2-{3-[2-(1-piperidyl)ethoxy]-2-pyridyl}-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(75) 2-{3-[2-(1-pyrrolidinyl)ethoxy]-2-pyridyl}-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(76) 2-{3-[2-(1-methyl-2-pyrrolidinyl)ethoxy]-2-pyridyl}-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(77) 2-[3-(2-dimethylaminoethoxy)-2-pyridyl]-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(78) 2-(3-aminophenyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(79) 2-(2-aminophenyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(80) 2-phenyl-4-(tetrahydro-4H-pyran-4-yl)-4H-1,3,4-oxadiazine-5(6H)-one,

(81) 2-phenyl-4-(1-methyl-4-piperidyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(82) 2-phenyl-4-(3-quinuclidinyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(83) 2-pyridyl-4-(1-benzyl-4-piperidyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(84) 2-phenyl-4-(3-tetrahydrofuranyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(85) 2-phenyl-4-cyclopentyl-4H-1,3,4-oxadiazine-5(6H)-one,

(86) 2-phenyl-4-(1-benzyl-4-piperidyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(87) 2-phenyl-4-[1-(2-pyridyl)ethyl]-4H-1,3,4-oxadiazine-5(6H)-one,

(88) 2-phenyl-4-[1-(3-pyridyl)ethyl]-4H-1,3,4-oxadiazine-5(6H)-one,

(89) 2-phenyl-4-[1-(4-pyridyl)ethyl]-4H-1,3,4-oxadiazine-5(6H)-one,

(90) 2-(3-dimethylaminophenyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(91) 2-(2-dimethylaminophenyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(92) 2-[2-(4-pyridyl)methylaminophenyl]-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(93) 2-[2-(3-pyridyl)methylaminophenyl]-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(94) 2-(4-pyridyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(95) N-(2-pyridyl)-[4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one-2-yl]carboxamide,

(96) N-(3-pyridyl)-[4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one-2-yl]carboxamide,

(97) N-(4-pyridyl)-[4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one-2-yl]carboxamide,

(98) 1,3-diphenyl-4-methyl-4,5-dihydro-1,2,4-triazine-6(1H)-one and

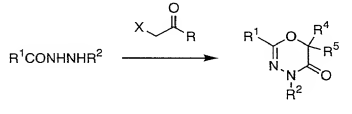
(99) 1-phenyl-3-(2-pyridyl)-4-methyl-4,5-dihydro-1,2,4-triazine-6(1H)-one.

The "salt" and "pharmacologically acceptable salt" in the

present invention are not limited insofar as they are salts formed with the heterodiazinon compound of the present invention, and such salts include e.g. hydrohalogenic acid salts such as hydrofluorate, hydrochloride, hydrobromate and hydroiodate; inorganic acid salts such as sulfate, nitrate, perchlorate, phosphate, carbonate and bicarbonate; organic carboxylic acid salts such as acetate, maleate, tartrate and fumarate; organic sulfonic acid salts such as methane sulfonate, trifluoromethane sulfonate, ethane sulfonate, benzene sulfonate, toluene sulfonate and camphor sulfonate; amino acid salts such as aspartate and glutamate; amine salts such as trimethylamine salt, triethylamine salt, procaine salt, pyridine salt and phenetyl benzyl amine salt; alkali metal salts such as sodium salt and potassium salt; and alkaline earth metal salts such as magnesium salt and calcium salt, and preferable examples are hydrochloride and oxalate.

Various processes can be used for producing the compounds of the present invention, and the typical examples are as follows:

1. A hydrazide compound having substituent groups R^1 and R^2 is cyclized



In this reaction scheme, A, R^1, R^2, R^4 and R^5 have the same

meanings as defined above, X represents halogen atom, and R represents hydroxyl group or a halogen atom. In this reaction, a known hydrazine compound is reacted with a halogenated acetate compound, to give a heterodiazinon compound. Herein, the halogenated acetate compound includes e.g. chloroacetyl chloride, bromoacetyl bromide etc.

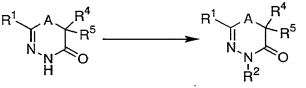
The reaction proceeds smoothly in the presence of a base. The base herein used includes, but is not limited to, potassium carbonate, sodium carbonate, sodium bicarbonate, sodium hydroxide, potassium hydroxide, triethylamine, pyridine, N,N-dimethyl aniline etc.

From the viewpoint of regulating operativeness, stirring and reaction temperature, this reaction is preferably carried out in the presence of a solvent. The solvent used is not particularly limited insofar as it is inert to the hydrazide compound, halogenated acetate compound or base, and specifically it includes e.g. acetone, 2-butanone (MEK, methyl ethyl ketone), 3-pentanone (diethyl ketone), 3-hexanone (ethyl propyl ketone), 4-heptanone (dipropyl ketone), 2,4-dimethyl-3-pentanone (diisopropyl ketone), formamide, N,N-dimethyl formamide (DMF), tetrahydrofuran (THF), 1,2-dimethoxyethane (DME, ethylene glycol dimethyl ether), ethyl ether, isopropyl ether, butyl ether, methyl acetate, ethyl acetate, propyl acetate, methyl propionate, ethyl propionate, methyl butyrate, ethyl butyrate, dimethyl carbonate, diethyl carbonate, dipropyl carbonate, methyl ethyl carbonate, 1,4-

dioxane, 1,3-dioxolane, nitromethane, 1-methyl-2-pyrrolidone, dimethyl sulfoxide (DMSO), hexamethyl phosphonamide (HMPA), acetonitrile, pyridine, triethylamine, N,N-dimethylaniline etc.

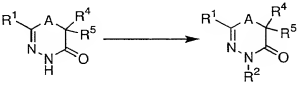
The reaction temperature is not limited, but usually by heating under reflux, the reaction is finished in a short time.

2. R^2 is introduced into a heterodiazinon compound having the substituent group R^1 (1)



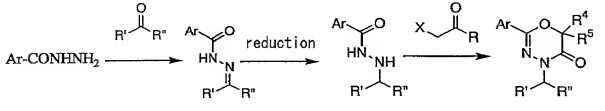
In the above scheme, A, R^1, R^2, R^4 and R^5 have the same meanings as defined above. In this reaction, a heterodiazinon compound is reacted with a halogen aryl compound, which can be conducted according to a conventional method in Ullmann reaction. Further, the reaction is conducted preferably in the presence of a base, and particularly potassium acetate gives better results. Further, this reaction can also be conducted by the coupling reaction of a heterodiazinon compound with an aryl boric acid compound using copper acetate in the presence of a base.

3. R^2 is introduced into a heterodiazinon compound having the substituent group R^1 (2)



In this scheme, A, R^1, R^2, R^4 and R^5 have the same meanings as defined above. Also in this reaction, a heterodiazinon compound is reacted with a halogen aryl compound, which can be conducted according to a conventional method of N-alkylation in the presence of a base or in a usual manner by KOEN reaction.

4. When the substituent group R^2 is a lower alkyl group, an imine is reduced and then cyclized



In this reaction scheme, X represents a halogen atom, R represents hydroxyl group or a halogen atom, Ar represents an optionally substituted aryl group, and R' and R" are the same as or different from each other and each represents a lower alkyl group. In this reaction, an imine is synthesized from e.g. a benzoyl hydrazine compound and ketone, and then reduced and reacted with a halogenated acetate derivative, to give a heterodiazinon compound. The reducing agent used includes e.g. lithium aluminum hydride, sodium borohydride, sodium triacetoxysetoxy borohydride, sodium cyanoborohydride, etc.

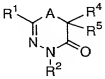
In addition to the methods described above, the substituent groups R^1 and R^2 can also be modified to derive new compounds.

The foregoing is the process for producing Compound (I) etc. of the present invention, and the starting compound in the

above reaction may have formed a salt or a hydrate insofar as the reaction is not inhibited. If the compounds of the present invention are obtained in free form, they can be converted in a usual manner into salts which may be formed by Compound (1) etc. The resulting various isomers of the compounds of the present invention can be isolated and purified by conventional separation techniques (e.g., re-crystallization, chromatography etc.).

As the pharmaceutical preparation, the compounds of the present invention, that is, the compound represented by the formula (I) below, a pharmacologically acceptable salt thereof or hydrates thereof and the heterodiazinon compound represented by the formula (V) below, a pharmaceutically acceptable salt thereof, as well as a composition comprising these, are useful as an agent for preventing, treating and ameliorating diseases against which non-N-methyl-D-aspartate excitatory antagonistic action is effective, specifically as an agent for preventing, treating and ameliorating diseases against which 2-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid excitatory amino acid receptor antagonistic action is effective, more specifically as an agent for preventing, treating and ameliorating nerve degeneration diseases, and further specifically as an agent for preventing, treating and ameliorating 1) disturbance such as motor disturbance, hindrance of sensibility and abnormal behavior, caused by disturbance after cerebral ischemia and acute nerve

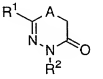
degeneration after cerebrospinal injuries; 2) chronic nerve degeneration diseases such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis and Huntington's chorea; 3) epilepsy; 4) chronic pain, migraine, cancerous pain and pain originating in diabetic nerve disturbance; 5) spastic paralysis or 6) demyelinating diseases such as multiple sclerosis, encephalomyelitis, Guillain Barre syndrome, Marchiafava Bignami disease, Devic disease, Balo disease, REFSAME disease, TANGIEL disease, DEJERIN-SOTAS disease, HIV or HTLV myelopathy, and leukoencephalopathy.



(I)

In the formula, A represents oxygen, sulfur or a group represented by the formula $>NR^3$ (wherein R^3 represents hydrogen atom or a lower alkyl group; R^1 and R^2 are the same as or different from each other and each represents an optionally substituted aryl group, an optionally substituted heteroaryl group, an optionally substituted aralkyl group, an optionally substituted heteroaryl alkyl group, an optionally substituted aryl alkenyl group, an optionally substituted heteroaryl alkenyl group, an optionally substituted piperidyl group, an optionally substituted piperazinyl group, a morpholinyl group, an optionally substituted lower cycloalkyl group, a tetrahydrofuranyl group, a tetrahydropyranyl group, an adamantyl group, an optionally substituted amino group or an

optionally substituted amide group; and R^4 and R^5 are the same as or different from each other and each represents hydrogen atom, hydroxyl group, a halogen atom, nitrile group, nitro group, a lower alkyl group, an aryl group or a heteroaryl group.



(V)

In the formula, A represents oxygen, sulfur or a group represented by the formula $>NR^3$ (wherein R^3 represents hydrogen atom or a lower alkyl group); and R^1 and R^2 are the same as or different from each other and each represents an optionally substituted aryl group, an optionally substituted heteroaryl group, an optionally substituted aralkyl group, an optionally substituted heteroaryl alkyl group, an optionally substituted aryl alkenyl group, an optionally substituted heteroaryl alkenyl group, an optionally substituted piperidyl group, an optionally substituted piperazinyl group, a morpholinyl group, an optionally substituted lower cycloalkyl group, a tetrahydrofuranyl group, a tetrahydropyranyl group, an adamantyl group, an optionally substituted amino group or an optionally substituted amide group.

The heterodiazinon compound (V) above encompasses compounds disclosed in the above-mentioned US-4,670,555 (US-4,782,066). Specifically, the heterodiazinon compound (V) includes, but is not limited to, the similar compound as described for the heterodiazinon compound (I).

Compound (I) according to the present invention can be formed in a usual manner into tablets, powders, fine powders, granules, coated tablets, capsules, syrups, troches, inhalations, suppositories, injections, ointments, eye ointments, eye drops, nose drops, ear drops, poultices and lotions. These pharmaceutical preparations are produced in a usual manner by blending generally used ingredients as starting materials, where ordinarily used excipients, binders, lubricants, coloring agents, taste and odor correctives and as necessary stabilizers, emulsifiers, absorption promoters, surfactants, pH adjusters, preservatives and antioxidants can be used for pharmaceutical manufacturing. That is, when an oral preparation is produced, the heterodiazinon compound or a pharmacologically acceptable salt thereof and excipients and as necessary a binder, an disintegrating agent, a lubricant, a coloring agent, taste and odor correctives etc. are added and formed in a usual manner into powders, fine powders, granules, tablets, coated tablets, capsules etc. These ingredients include e.g. animal and vegetable oils such as soybean oil, tallow and synthetic glyceride; hydrocarbons such as liquid paraffin, squalane and solid paraffin; ester oils such as octyldodecyl myristate and isopropyl myristate; higher alcohols such as cetostearyl alcohol and behenyl alcohol; silicon resin; silicon oil; surfactants such as polyoxyethylene fatty ester, sorbitan fatty ester, glycerin fatty ester, polyoxyethylene sorbitan fatty ester, polyoxyethylene

hardened castor oil and polyoxyethylene/polyoxypropylene block copolymer; water-soluble polymers such as hydroxy ethyl cellulose, polyacrylic acid, carboxyvinyl polymer, polyethylene glycol, polyvinyl pyrrolidone and methyl cellulose; lower alcohols such as ethanol and isopropanol; polyvalent alcohols such as glycerin, propylene glycol, dipropylene glycol and sorbitol; sugars such as glucose and sucrose; and inorganic powder such as silicic anhydride, aluminum magnesium silicate and aluminum silicate, and pure water. The excipients include e.g. lactose, corn starch, white sugar, glucose, mannitol, sorbitol, crystalline cellulose, silicon dioxide etc.; the binder includes e.g. polyvinyl alcohol, polyvinyl ether, methyl cellulose, ethyl cellulose, gum arabia, tragacanth, gelatin, shellac, hydroxy propyl methyl cellulose, hydroxy propyl cellulose, polyvinyl pyrrolidone, polypropylene glycol-polyoxyethylene block polymer, megulumin etc.; the disintegrating agent includes e.g. starch, agar, gelatin powder, crystalline cellulose, calcium carbonate, sodium bicarbonate, calcium citrate, dextrin, pectin, carboxymethyl cellulose calcium etc.; the lubricant includes e.g. magnesium stearate, talc, polyethylene glycol, silica, hardened vegetable oil etc.; the coloring agent includes e.g. those coloring agents approved to be added to pharmaceutical preparations; and the taste and odor correctives include cocoa powder, menthol, aromatic powder, peppermint oil, borneol, cinnamon powder etc. These tablets and granules may be coated

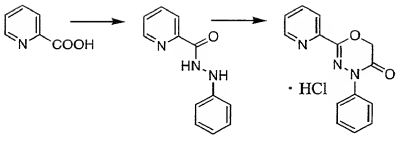
as necessary. When the injection preparation is produced, a pH adjuster, a solubilizer and an isotonizing agent together with a solubilizing aid and a stabilizer as necessary may be added to the heterodiazinon compound or a pharmacologically acceptable salt thereof, which is then formed in a usual manner into an injection. An agent for external application can be produced in any conventional method. That is, the starting base material used in manufacturing can make use of various starting materials ordinarily used in pharmaceutical preparations, non-pharmaceutical preparations, cosmetics etc. Specifically, the starting base material includes e.g. animal and vegetable oils, mineral oil, ester oil, waxes, higher alcohols, fatty acids, silicon oil, surfactants, phospholipids, alcohols, polyvalent alcohols, water-soluble polymers, clay minerals, pure water etc. As necessary, a pH adjuster, an antioxidant, a chelating agent, a preservative, a coloring agent, a perfume etc. can further be added. However, the starting base material of the present agent for external application is not limited thereto. Further, ingredients having differentiation-inducing action, a blood-stream promoter, a sterilizer, an anti-inflammatory agent, a cell activator, vitamins, amino acids, a humectant, a keratin solubilizer etc. can also be incorporated as necessary. The amount of the starting base material added is usually an amount for achieving a concentration predetermined for producing the agent for external application.

When Compound (I) of the present invention is administered as a pharmaceutical preparation, it can be orally or parenterally administered in any form in a usual manner. For example, it can be formed into, and administered as, tablets, powders, granules, capsules, syrups, troches, inhalations, suppositories, injections, ointments, eye ointments, eye drops, nose drops, ear drops, poultices and lotions. Although the dose of the pharmaceutical preparation of the present invention is varied depending on the severeness of symptoms, age, sex, body weight, administration form and the type of disease, the pharmaceutical preparation is administered into a man in one portion or in divided portions in a daily dose of usually about 0.01 mg to 2000 mg, preferably 0.1 mg to 1000 mg, more preferably 0.5 mg to 500 mg.

Examples

The following examples (salts and hydrates thereof, and pharmaceutical compositions containing them) and test examples are illustrative, and not intended to limit the compounds of the present invention. Those skilled in the art can carry out the present invention at the maximum degree by adding various modifications not only to the following examples but also to the claims in the present specification, and such modifications are included in the claims in the present specification.

Example 1. 2-(2-Pyridyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one hydrochloride



1-1) Phenyl hydrazide nicotinate

In a nitrogen atmosphere, picolinic acid (6.83 g) was dissolved in a mixed solvent of dimethyl formamide/tetrahydrofuran (1:1, 00ml), and 1,1-carbonyl diimidazole (9.90 g) was added thereto. After stirring at room temperature for 30 minutes, phenyl hydrazine (6.00 g) was added thereto and further stirred overnight at room temperature. Water was added to the reaction solution, and the resulting solid was separated by filtration and dried, to give the title compound (10.1 g, 86 %).

^{1}H-NMR (400MHz, DMSO-d_6) ; δ (ppm) 6.66-6.70 (m, 1H), 6.70-6.75 (m, 2H), 7.08-7.14 (m, 2H), 7.61-7.64 (m, 1H), 7.81-7.89 (m, 1H), 7.98-8.01 (m, 2H), 8.65-8.68 (m, 1H), 10.51-10.54 (m, 1H).

1-2) 2-(2-Pyridyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one hydrochloride

Phenyl hydrazide nicotinate (10.1 g) obtained in 1-1) was dissolved in methyl ethyl ketone (250 ml). Chloroacetyl chloride (3.77 ml) was added thereto, followed by heating under reflux for 1 hour. After the solution was left and cooled to room temperature, potassium carbonate (39.4 g) was added thereto and refluxed for 3 hours under heating. The reaction

solution was left and cooled to room temperature, evaporated, diluted with ethyl acetate, washed with water and brine, and then dried over anhydrous magnesium sulfate. After the drying agent was filtered off, the product was evaporated, and the resulting crystalline residues were recrystallized from ethyl acetate/hexane and then from methanol/hexane, to give the title compound in a free form (6.80 g, 57 %).

Free compound

^{1}H-NMR (400MHz, $CDCl_3$) ; δ (ppm) 4.98 (s, 2H), 7.32 (tt, 1H), 7.40 (ddd, 1H), 7.43-7.49 (m, 2H), 7.68-7.72 (m, 2H), 7.79 (ddd, 1H), 8.06-8.09 (m, 1H), 8.71-8.74 (m, 1H).

This free compound (6.60 g) was converted into a hydrochloride with 4N hydrochloric acid/ethyl acetate solution, and recrystallized from ethanol/tetrahydrofuran/ethyl acetate, to give the title compound (6.51 g).

Hydrochloride

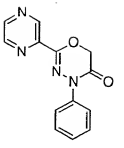
^{1}H-NMR (400MHz, DMSO-d_6) ; δ (ppm) 5.04 (s, 2H), 7.30-7.36 (m, 1H), 7.45-7.51 (m, 2H), 7.56 (ddd, 1H), 7.65-7.70 (m, 2H), 7.96 (ddd, 1H), 7.99-8.03 (m, 1H), 8.66-8.70 (m, 1H).

ESI-mass ; 254 (MH^+)

m.p. ; 149-150℃

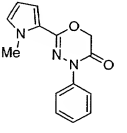
The compounds in the following Examples 2 to 16 were synthesized in the same manner as in Example 1.

Example 2. 2-(2-Pyrazinyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one



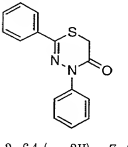
^{1}H-NMR (400MHz, DMSO-d_6) ; δ (ppm) 5.06 (s, 2H), 7.29-7.35 (m, 1H), 7.44-7.49 (m, 2H), 7.65-7.69 (m, 4H), 8.73-8.77 (m, 2H), 9.17-9.19 (m, 1H).

Example 3. 2-(1-Methyl-2-pyrolyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one



^{1}H-NMR (400MHz, DMSO-d_6) ; δ (ppm) 3.82 (s, 3H), 4.87 (s, 2H), 6.07-6.13 (m, 1H), 6.63-6.68 (m, 1H), 7.01-7.06 (m, 1H), 7.23-7.30 (m, 1H), 7.39-7.48 (m, 2H), 7.63-7.71 (m, 2H).

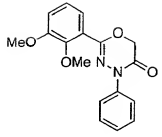
Example 4. 2,4-Diphenyl-4H-1,3,4-thiadiazine-5(6H)-one



^{1}H-NMR (400MHz, $CDCl_3$) ; δ (ppm) 3.64 (s, 2H), 7.30-7.37 (m, 1H), 7.40-7.51 (m, 5H), 7.53-7.59 (m, 2H), 7.87-7.94 (m, 2H).

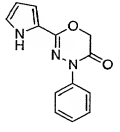
ESI-mass ; 269 (MH^+)

Example 5. 2-(2,3-Dimethoxyphenyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one



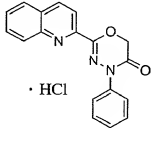
^{1}H-NMR (400MHz, DMSO-d_6) ; δ (ppm) 3.77 (s, 3H), 3.82 (s, 3H), 4.96 (s, 2H), 7.12-7.18 (m, 2H), 7.19-7.23 (m, 1H), 7.25-7.30 (m, 1H), 7.40-7.46 (m, 2H), 7.61-7.65 (m, 2H).

Example 6. 2-(2-Pyrolyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one



^{1}H-NMR (400MHz, DMSO-d_6) ; δ (ppm) 4.88 (s, 2H), 6.13-6.17 (m, 1H), 6.58-6.62 (m, 1H), 6.93-6.97 (m, 1H), 7.24-7.30 (m, 1H), 7.40-7.47 (m, 2H), 7.72-7.77 (m, 2H).

Example 7. 2-(2-Quinolyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one hydrochloride

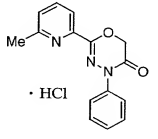


Free compound

^{1}H-NMR (400MHz, DMSO-d_6) ; δ (ppm) 5.09 (s, 2H), 7.31-7.37 (m, 1H), 7.46-7.52 (m, 2H), 7.66-7.73 (m, 3H), 7.80-7.85 (m, 1H), 8.02-8.06 (m, 1H), 8.09-8.15 (m, 2H), 8.44-8.48 (m, 1H).

ESI-mass ; 304 (MH^+)

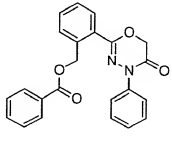
Example 8. 2-(6-Methyl-2-pyridyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one hydrochloride



Free compound

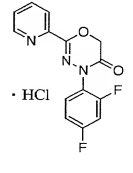
^{1}H-NMR (400MHz, DMSO-d_6) ; δ (ppm) 2.50 (s, 3H), 5.00 (s, 2H), 7.29-7.33 (m, 1H), 7.36-7.39 (m, 1H), 7.43-7.48 (m, 2H), 7.62-7.66 (m, 2H), 7.78-7.80 (m, 2H).

Example 9. 2-Benzoyloxymethyl-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one



^{1}H-NMR (400MHz, $CDCl_3$) ; δ (ppm) 4.86 (s, 2H), 5.71 (s, 2H), 7.25-7.31 (m, 1H), 7.38-7.47 (m, 5H), 7.48-7.62 (m, 3H), 7.66-7.70 (m, 2H), 7.85-7.89 (m, 1H), 8.05-8.09 (m, 2H).

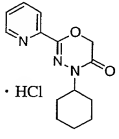
Example 10. 2-(2-Pyridyl)-4-(2,4-difluorophenyl)-4H-1,3,4-oxadiazine-5(6H)-one hydrochloride



Free compound

^{1}H-NMR (400MHz, DMSO-d_6) ; δ (ppm) 5.08 (s, 2H), 7.21-7.27 (m, 1H), 7.47 (ddd, 1H), 7.51 (ddd, 1H), 7.65 (ddd, 1H), 7.86-7.92 (m, 2H), 8.64 (ddd, 1H).

Example 11. 2-(2-Pyridyl)-4-cyclohexyl-4H-1,3,4-oxadiazine-5(6H)-one hydrochloride



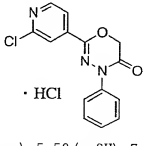
· HCl

Free compound

^{1}H-NMR (400MHz, DMSO-d_6) ; δ (ppm) 1.06-1.22 (m, 1H), 1.34 (ddt, 2H), 1.57-1.83 (m, 7H), 4.33-4.41 (m, 1H), 4.81 (s, 2H), 7.48 (ddd, 1H), 7.87-7.96 (m, 2H), 8.62 (ddd, 1H).

ESI-mass ; 260 (MH^+)

Example 12. 2-(2-Chloro-4-pyridyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one hydrochloride

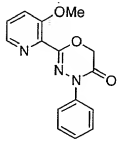


· HCl

^{1}H-NMR (400MHz, DMSO-d_6) ; δ (ppm) 5.50 (s, 2H), 7.29-7.34 (m, 1H), 7.44-7.48 (m, 2H), 7.63-7.66 (m, 2H), 7.76 (d, 1H), 7.78 (s, 1H), 8.53 (d, 1H).

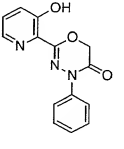
ESI-mass ; 288 (MH^+)

Example 13. 2-(3-Methoxy-2-pyridyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one



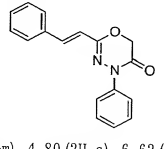
^{1}H-NMR (400MHz, $CDCl_3$) ; δ (ppm) 3.95 (s, 3H), 4.95 (s, 2H), 7.25-7.29 (m, 1H), 7.34-7.44 (m, 4H), 7.70-7.73 (m, 2H), 8.31 (d, 1H).

Example 14. 2-(3-Hydroxy-2-pyridyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one



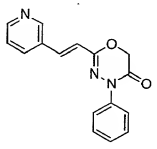
^{1}H-NMR (400MHz, $CDCl_3$) ; δ (ppm) 5.07 (s, 2H), 7.26-7.39 (m, 3H), 7.47-7.51 (m, 2H), 7.57-7.60 (m, 2H), 8.30-8.32 (m, 1H), 10.51 (s, 1H).

Example 15. 2-Styryl-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one



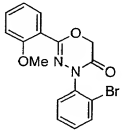
^{1}H-NMR (400MHz, $CDCl_3$) ; δ (ppm) 4.80 (2H, s), 6.62 (1H, d), 7.28-7.50 (9H, m), 7.63 (2H, d).

Example 16. 2-[2-(3-Pyridyl)vinyl]-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one



^{1}H-NMR (400MHz, $CDCl_3$) ; δ (ppm) 4.83 (2H, s), 6.67 (1H, d), 7.30-7.50 (4H, m), 7.63 (2H, m), 7.63 (2H, m), 7.84 (1H, d), 8.57 (1H, d), 8.72 (1H, br).

Example 17. 2-(2-Methoxyphenyl)-4-(2-bromophenyl)-4H-1,3,4-oxadiazine-5(6H)-one



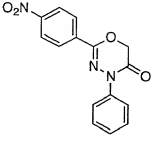
2-Bromophenyl hydrazine hydrochloride (105 g) was dissolved in a mixed solvent of pyridine/dimethyl formamide (1:1, 1000 ml). Under ice-cooling, m-anisoyl chloride (76.7 g) was added thereto, followed by stirring overnight at room temperature. The reaction solution was diluted with ethyl acetate, washed with water, 1N hydrochloric acid, an aqueous saturated sodium bicarbonate solution and brine, and dried over anhydrous magnesium sulfate. After the drying agent was filtered off, the reaction solution was evaporated, to give a hydrazide compound. Then it was treated in the same manner as in Example 1-2, to give the title compound (126 g, 74 %).

^{1}H-NMR (400MHz, $CDCl_3$) ; δ (ppm) 3.88 (s, 3H), 4.89 (s, 2H), 6.94-6.99 (m, 2H), 7.25-7.30 (m, 1H), 7.39-7.45 (m, 2H), 7.48 (dd, 1H), 7.55-7.59 (m, 1H),

7. 69 (dd, 1H).

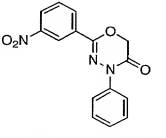
The following compounds in Examples 18 to 35 were synthesized in the same manner as in Example 17.

Example 18. 2-(4-Nitrophenyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one



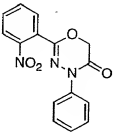
^{1}H-NMR (400MHz, DMSO-d_6) ; δ (ppm) 5. 05 (s, 2H), 7. 28-7. 34 (m, 1H), 7. 42-7. 49 (m, 2H), 7. 62-7. 68 (m, 2H), 8. 05-8. 11 (m, 2H), 8. 27-8. 32 (m, 2H).

Example 19. 2-(3-Nitrophenyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one



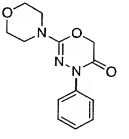
^{1}H-NMR (400MHz, $CDCl_3$) ; δ (ppm) 4. 96 (s, 2H), 7. 31-7. 37 (m, 1H), 7. 44-7. 51 (m, 2H), 7. 60-7. 66 (m, 1H), 7. 68-7. 72 (m, 2H), 8. 26-8. 30 (m, 1H), 8. 31-8. 35 (m, 1H), 8. 75-8. 77 (m, 1H).

Example 20. 2-(2-Nitrophenyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one



^{1}H-NMR (400MHz, $CDCl_3$) ; δ (ppm) 4.82 (s, 2H), 7.28-7.34 (m, 1H), 7.43-7.48 (m, 2H), 7.62-7.72 (m, 4H), 7.81-7.85 (m, 1H), 7.95-7.99 (m, 1H).

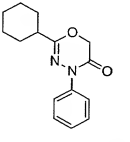
Example 21. 2-(4-Morpholinyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one



^{1}H-NMR (400MHz, DMSO-d_6) ; δ (ppm) 3.38-3.44 (m, 4H), 3.60-3.66 (m, 4H), 5.00 (s, 2H), 7.08-7.13 (m, 1H), 7.14-7.19 (m, 2H), 7.33-7.39 (m, 2H).

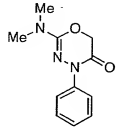
ESI-mass ; 262 (MH^+)

Example 22. 2-Cyclohexyl-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one



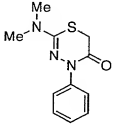
^{1}H-NMR (400MHz, $CDCl_3$) ; δ (ppm) 1.16-1.36 (m, 3H), 1.40-1.52 (m, 2H), 1.64-1.72 (m, 1H), 1.76-1.84 (m, 2H), 1.90-1.99 (m, 2H), 2.34 (tt, 1H), 4.65 (s, 2H), 7.21-7.26 (m, 1H), 7.37-7.41 (m, 2H), 7.63-7.67 (m, 2H).

Example 23. 2-Dimethylamino-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one



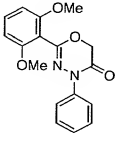
^{1}H-NMR (400MHz, DMSO-d_6) ; δ (ppm) 2.87-2.94 (m, 6H), 4.95 (s, 2H), 7.06-7.12 (m, 1H), 7.13-7.18 (m, 2H), 7.32-7.37 (m, 2H).

Example 24. 2-Dimethylamino-4-phenyl-4H-1,3,4-thiadiazine-5(6H)-one



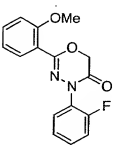
^{1}H-NMR (400MHz, $CDCl_3$) ; δ (ppm) 2.99 (s, 6H), 3.61 (s, 2H), 7.16-7.21 (m, 1H), 7.32-7.38 (m, 2H), 7.50-7.54 (m, 2H).

Example 25. 2-(2,6-Dimethoxyphenyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one



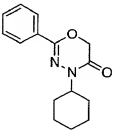
^{1}H-NMR (400MHz, DMSO-d_6) ; δ (ppm) 3.78 (s, 6H), 4.85 (s, 2H), 6.73 (d, 2H), 7.23-7.28 (m, 1H), 7.37-7.45 (m, 3H), 7.53-7.57 (m, 2H).

Example 26. 2-(2-Methoxy phenyl)-4-(2-fluorophenyl)-4H-1,3,4-oxadiazine-5(6H)-one



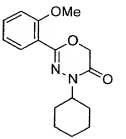
^{1}H-NMR (400MHz, $CDCl_3$) ; δ (ppm) 3.89 (s, 3H), 4.88 (s, 2H), 6.94-7.00 (m, 2H), 7.16-7.26 (m, 2H), 7.32-7.39 (m, 1H), 7.41-7.46 (m, 1H), 7.47-7.53 (m, 1H), 7.53-7.56 (m, 1H).

Example 27. 2-Phenyl-4-cyclohexyl-4H-1,3,4-oxadiazine-5(6H)-one



^{1}H-NMR (400MHz, DMSO-d_6) ; δ (ppm) 1.11-1.20 (m, 1H), 1.26-1.40 (m, 2H), 1.50-1.83 (m, 7H), 4.31-4.40 (m, 1H), 4.79 (s, 2H), 7.43-7.52 (m, 3H), 7.77-7.82 (m, 2H).
ESI-mass ; 259 (MH^+)

Example 28. 2-(2-Methoxyphenyl)-4-cyclohexyl-4H-1,3,4-oxadiazine-5(6H)-one

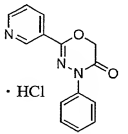


^{1}H-NMR (400MHz, DMSO-d_6) ; δ (ppm) 1.02-1.15 (m, 1H), 1.25-1.38 (m, 2H), 1.55-1.68 (m, 5H), 1.71-1.80 (m, 2H), 3.80 (s, 3H), 4.29-4.38 (m, 1H), 4.68 (s, 2H),

6.99 (ddd, 1H), 7.10 (d, 1H), 7.42-7.49 (m, 2H).

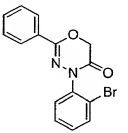
ESI-mass ; 289 (MH^+)

Example 29. 2-(3-Pyridyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one hydrochloride



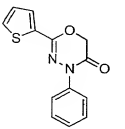
^{1}H-NMR (400MHz, DMSO-d_6) ; δ (ppm) 5.05 (s, 2H), 7.28-7.33 (m, 1H), 7.44-7.48 (m, 2H), 7.61 (t, 1H), 7.66-7.69 (m, 2H), 8.30 (d, 1H), 8.74 (d, 1H), 9.06 (s, 1H).

Example 30. 2-Phenyl-4-(2-bromophenyl)-4H-1,3,4-oxadiazine-5(6H)-one



^{1}H-NMR (400MHz, $CDCl_3$) ; δ (ppm) 4.94 (s, 2H), 7.28-7.33 (m, 1H), 7.38-7.49 (m, 5H), 7.71 (d, 1H), 7.87-7.90 (m, 2H).

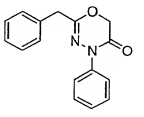
Example 31. 2-(2-Thienyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one



^{1}H-NMR (400MHz, $CDCl_3$) ; δ (ppm) 4.86 (2H, s), 7.08 (1H, m), 7.30 (1H, t), 7.40-

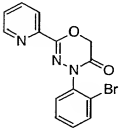
7. 50 (3H, m), 7. 56 (1H, s), 7. 70 (2H, d).

Example 32. 2-Benzyl-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one



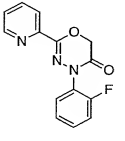
^{1}H-NMR (400MHz, $CDCl_3$) ; δ (ppm) 3. 64 (2H, s), 4. 63 (2H, s), 7. 25-7. 45 (8H, m), 7. 63 (2H, d).

Example 33. 2-(2-Pyridyl)-4-(2-bromophenyl)-4H-1,3,4-oxadiazine-5(6H)-one



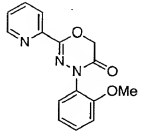
^{1}H-NMR (400MHz, $CDCl_3$) ; δ (ppm) 5. 02 (2H, s), 7. 30-7. 50 (4H, m), 7. 70 (1H, d), 7. 76 (1H, t), 7. 99 (1H, d), 8. 70 (1H, d).

Example 34. 2-(2-Pyridyl)-4-(2-fluorophenyl)-4H-1,3,4-oxadiazine-5(6H)-one



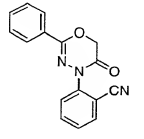
^{1}H-NMR (400MHz, $CDCl_3$) ; δ (ppm) 5. 02 (2H, s), 7. 20-7. 30 (2H, m), 7. 36-7. 43 (2H, m), 7. 50 (1H, t), 7. 77 (1H, t), 8. 00 (1H, d), 8. 72 (1H, d).

Example 35. 2-(2-Pyridyl)-4-(2-methoxyphenyl)-4H-1,3,4-oxadiazine-5(6H)-one



^{1}H-NMR (400MHz, $CDCl_3$) ; δ (ppm) 3.85 (3H, s), 5.00 (2H, s), 7.00-7.10 (2H, m), 7.34-7.43 (3H, m), 7.72 (1H, t), 7.98 (1H, d), 8.70 (1H, d).

Example 36 2-Phenyl-4-(2-cyanophenyl)-4H-1,3,4-oxadiazine-5(6H)-one

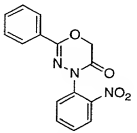


In 100 ml 1,2-dichlorobenzene were dissolved 7.01 g 2-phenyl-4H-1,3,4-oxadiazine-5(6H)-one synthesized according to Receuil des Travaux chimiques des Pays Bas, 1929, 48, 417 and 14.67 g 2-bromobenzonitrile, followed by adding 11.85 g potassium acetate and 5.15 g copper. The mixture was heated at 190 °C for 2 hours under vigorous stirring. After the reaction solution was left and cooled to room temperature, it was poured into water. The mixture was extracted with ethyl acetate, and the insoluble matters were separated by filtration, followed by drying over anhydrous magnesium sulfate. The solvent was evaporated, and the residue was purified by silica gel column chromatography (hexane/ethyl acetate system). The resulting crude crystals were recrystallized from ethyl acetate/hexane, to give 1.12 g title compound (yield, 10 %).

^{1}H-NMR (400MHz, $CDCl_3$) ; δ (ppm) 4.94 (s, 2H), 7.39-7.51 (m, 4H), 7.65-7.74 (m, 2H), 7.77-7.80 (m, 1H), 7.91-7.95 (m, 2H).

m.p. ; 148-149℃

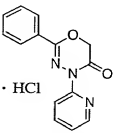
Example 37. 2-Phenyl-4-(2-nitrophenyl)-4H-1,3,4-oxadiazine-5(6H)-one



^{1}H-NMR (400MHz, DMSO-d_6) ; δ (ppm) 5.06 (s, 2H), 7.45-7.57 (m, 3H), 7.62-7.68 (m, 1H), 7.77-7.89 (m, 4H), 8.06 (dd, 1H).

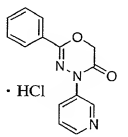
ESI-mass ; 298 (MH^+)

Example 38. 2-Phenyl-4-(2-pyridyl)-4H-1,3,4-oxadiazine-5(6H)-one hydrochloride



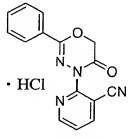
^{1}H-NMR (400MHz, DMSO-d_6) ; δ (ppm) 5.04 (s, 2H), 7.40-7.52 (m, 4H), 7.61 (d, 1H), 7.82-7.84 (m, 2H), 7.97 (td, 1H), 8.56 (dd, 1H).

Example 39. 2-Phenyl-4-(3-pyridyl)-4H-1,3,4-oxadiazine-5(6H)-one hydrochloride



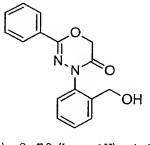
^{1}H-NMR (400MHz, DMSO-d_6) ; δ (ppm) 5.08 (s, 2H), 7.48-7.58 (m, 3H), 7.72-7.79 (m, 1H), 7.91-7.94 (m, 2H), 8.40-8.49 (m, 1H), 8.60-8.61 (m, 1H), 9.12 (s, 1H).

Example 40. 2-Phenyl-4-(3-cyano-2-pyridyl)-4H-1,3,4-oxadiazine-5(6H)-one hydrochloride



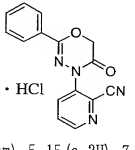
^{1}H-NMR (400MHz, DMSO-d_6) ; δ (ppm) 5.18 (s, 2H), 7.46-7.50 (m, 2H), 7.52-7.57 (m, 1H), 7.73 (dd, 1H), 7.82-7.85 (m, 2H), 8.56 (dd, 1H), 8.89 (dd, 1H).

Example 41. 2-Phenyl-4-(2-hydroxymethylphenyl)-4H-1,3,4-oxadiazine-5(6H)-one



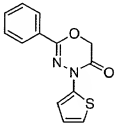
^{1}H-NMR (400MHz, $CDCl_3$) ; δ (ppm) 2.70 (brs, 1H), 4.59 (s, 2H), 4.93 (s, 2H), 7.37-7.50 (m, 6H), 7.56-7.60 (m, 1H), 7.84-7.87 (m, 2H).

Example 42. 2-Phenyl-4-(2-cyano-3-pyridyl)-4H-1,3,4-oxadiazine-5(6H)-one hydrochloride



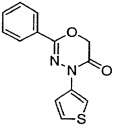
^{1}H-NMR (400MHz, DMSO-d_6) ; δ (ppm) 5.15 (s, 2H), 7.47-7.57 (m, 3H), 7.86-7.88 (m, 2H), 7.92 (dd, 1H), 8.28 (dd, 1H), 8.75 (dd, 1H).

Example 43. 2-Phenyl-4-(2-thienyl)-4H-1,3,4-oxadiazine-5(6H)-one



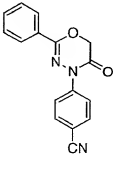
^{1}H-NMR (400MHz, $CDCl_3$) ; δ (ppm) 4.91 (s, 2H), 6.98 (dd, 1H), 7.02 (dd, 1H), 7.43-7.52 (m, 4H), 7.96-8.00 (m, 2H).

Example 44. 2-Phenyl-4-(3-thienyl)-4H-1,3,4-oxadiazine-5(6H)-one



^{1}H-NMR (400MHz, $CDCl_3$) ; δ (ppm) 4.85 (s, 2H), 7.31 (dd, 1H), 7.41-7.51 (m, 3H), 7.66 (dd, 1H), 7.77 (dd, 1H), 7.94-7.97 (m, 2H).

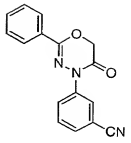
Example 45. 2-Phenyl-4-(4-cyanophenyl)-4H-1,3,4-oxadiazine-5(6H)-one



^{1}H-NMR (400MHz, $CDCl_3$) ; δ (ppm) 4.90 (s, 2H), 7.44-7.55 (m, 3H), 7.72-7.75 (m, 2H), 7.94-7.97 (m, 2H), 8.03-8.06 (m, 2H).

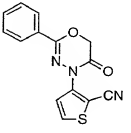
Example 46. 2-Phenyl-4-(3-cyanophenyl)-4H-1,3,4-oxadiazine-

5(6H)-one



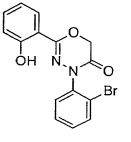
^{1}H-NMR (400MHz, $CDCl_3$) ; δ (ppm) 4.90 (s, 2H), 7.44-7.57 (m, 5H), 7.94-7.97 (m, 2H), 8.13-8.16 (m, 1H), 8.18-8.19 (m, 1H).

Example 47. 2-Phenyl-4-(2-cyano-3-thienyl)-4H-1,3,4-oxadiazine-5(6H)-one



^{1}H-NMR (400MHz, $CDCl_3$) ; δ (ppm) 4.89 (s, 2H), 7.43-7.50 (m, 3H), 7.54 (d, 1H), 7.77 (d, 1H), 8.06-8.09 (m, 2H).

Example 48. Synthesis of 2-(2-hydroxyphenyl)-4-(2-bromophenyl)-4H-1,3,4-oxadiazine-5(6H)-one



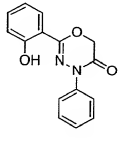
In methylene chloride (1000 ml) was dissolved 2-(2-methoxyphenyl)-4-(2-bromophenyl)-4H-1,3,4-oxadiazine-5(6H)-one (91.0 g) obtained in Example 17. Under ice-cooling, 1.0M boron tribromide/methylene chloride solution (900 ml) was added

dropwise thereinto over 1 hour, followed by stirring for 1 hour. By adding an aqueous saturated sodium bicarbonate to the reaction solution, the organic layer was separated, and then purified by Cromatorex NH silica gel chromatography (methylene chloride). The resulting crude crystals were recrystallized from methylene chloride/hexane, to give the title compound (62.8 g, 74 %).

^{1}H-NMR (400MHz, $CDCl_3$) ; δ (ppm) 4.99 (d, 2H), 6.90-6.98 (m, 2H), 7.32-7.42 (m, 2H), 7.43-7.50 (m, 2H), 7.70-7.76 (m, 2H), 10.23 (s, 1H).

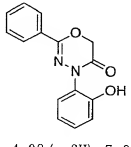
The following compounds in Examples 49 to 53 were synthesized in the same manner as in Example 48.

Example 49. 2-(2-Hydroxyphenyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one



^{1}H-NMR (400MHz, $CDCl_3$) ; δ (ppm) 4.94 (s, 2H), 6.91-6.97 (m, 2H), 7.00 (d, 1H), 7.32-7.43 (m, 2H), 7.47 (t, 2H), 7.57-7.63 (m, 2H), 7.73 (dd, 1H), 10.59 (s, 1H).

Example 50. 2-Phenyl-4-(2-hydroxyphenyl)-4H-1,3,4-oxadiazine-5(6H)-one

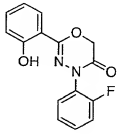


^{1}H-NMR (400MHz, $CDCl_3$) ; δ (ppm) 4.98 (s, 2H), 7.02-7.07 (m, 1H), 7.11 (dd, 1H),

7.26-7.32 (m, 1H), 7.42-7.47 (m, 2H), 7.49-7.54 (m, 1H), 7.58 (dd, 1H), 7.90-7.95 (m, 2H)

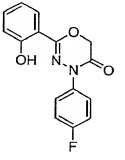
ESI-mass ; 269 (MH^+).

Example 51. 2-(2-Hydroxyphenyl)-4-(2-fluorophenyl)-4H-1,3,4-oxadiazine-5(6H)-one



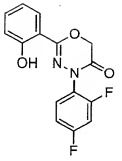
^{1}H-NMR (400MHz, $CDCl_3$) ; δ (ppm) 4.99 (s, 2H), 6.92-6.99 (m, 2H), 7.21-7.30 (m, 2H), 7.36-7.45 (m, 2H), 7.46-7.52 (m, 1H), 7.72 (dd, 1H), 10.30 (s, 1H).

Example 52. 2-(2-Hydroxyphenyl)-4-(4-fluorophenyl)-4H-1,3,4-oxadiazine-5(6H)-one



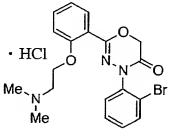
^{1}H-NMR (400MHz, $CDCl_3$) ; δ (ppm) 4.93 (s, 2H), 6.95 (ddd, 1H), 7.00 (dd, 1H), 7.13-7.19 (m, 2H), 7.37-7.43 (m, 1H), 7.54-7.60 (m, 2H), 7.72 (dd, 1H), 10.47 (s, 1H).

Example 53. 2-(2-Hydroxyphenyl)-4-(2,4-difluorophenyl)-4H-1,3,4-oxadiazine-5(6H)-one



^{1}H-NMR (400MHz, $CDCl_3$) ; δ (ppm) 4.99 (s, 2H), 6.92-7.04 (m, 4H), 7.39 (ddd, 1H), 7.44-7.50 (m, 1H), 7.72 (dd, 1H), 10.20 (s, 1H).

Example 54. 2-[2-(2-Dimethylamino)ethoxyphenyl]-4-(2-bromophenyl)-4H-1,3,4-oxadiazine-5(6H)-one hydrochloride



The compound in Example 48 (60.0 g) and N,N-dimethylaminoethyl chloride (37.2 g) were dissolved in dimethyl formamide (1000 ml). Potassium carbonate (35.8 g) was added thereto at 60 °C, followed by stirring overnight. The reaction solution was diluted with water and extracted with ether. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. After the drying agent was filtered off, the product was evaporated, to give a free compound (50.6 g, 70 %). This free compound (4.78 g) was converted into the hydrochloride in 4 N hydrochloric acid/ethyl acetate solution and recrystallized from ethanol/diethyl ether, to give the title compound (4.80 g).

Free compound

^{1}H-NMR (400MHz, $CDCl_3$) ; δ (ppm) 2.32 (s, 6H), 2.73 (t, 2H), 4.13 (t, 2H), 4.89 (s, 2H), 6.93-7.00 (m, 2H), 7.27-7.31 (m, 1H), 7.38-7.44 (m, 2H), 7.48 (dd, 1H), 7.58 (dd, 1H), 7.70 (dd, 1H).

Hydrochloride

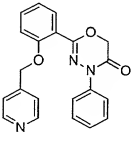
^{1}H-NMR (400MHz, DMSO-d_6) ; δ (ppm) 2.77 (s, 6H), 3.45-3.52 (m, 2H), 4.41 (t, 2H), 5.04 (s, 2H), 7.06-7.11 (m, 1H), 7.18-7.22 (m, 1H), 7.42 (ddd, 1H), 7.51-7.59 (m, 4H), 7.80 (dd, 1H).

ESI-mass ; 418, 420 (MH^+)

m.p. ; 169-170℃

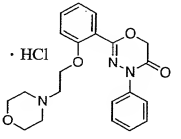
The following compounds in Examples 55 to 77 were synthesized in the same manner as in Example 54.

Example 55. 2-[2-(4-Pyridyl)methoxyphenyl]-4-phenyl-4 H-1,3,4-oxadiazine-5(6H)-one



^{1}H-NMR (400MHz, DMSO-d_6) ; δ (ppm) 4.97 (s, 2H), 5.24 (s, 2H), 7.07 (dd, 1H), 7.21 (d, 1H), 7.27-7.32 (m, 1H), 7.37-7.43 (m, 4H), 7.51 (ddd, 1H), 7.57-7.61 (m, 2H), 7.66 (dd, 1H), 8.40-8.43 (m, 2H).

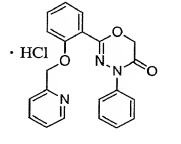
Example 56. 2-{2-[2-(4-Morpholinyl)ethoxy]phenyl}-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one hydrochloride



Free compound

^{1}H-NMR (400MHz, $CDCl_3$) ; δ (ppm) 2.50-2.56 (m, 4H), 2.82 (t, 2H), 3.65-3.72 (m, 4H), 4.18 (t, 2H), 4.84 (s, 2H), 6.95-7.04 (m, 2H), 7.25-7.31 (m, 1H), 7.39-7.46 (m, 3H), 7.59 (dd, 1H), 7.69-7.74 (m, 2H).

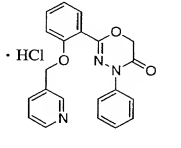
Example 57 2-[2-(2-Pyridyl)methoxyphenyl]-4-phenyl-4 H-1,3,4-oxadiazine-5(6H)-one hydrochloride



Free compound

^{1}H-NMR (400MHz, DMSO-d_6) ; δ (ppm) 4.93 (s, 2H), 5.24 (s, 2H), 7.06 (dd, 1H), 7.22-7.33 (m, 3H), 7.36-7.43 (m, 2H), 7.47-7.54 (m, 2H), 7.57-7.68 (m, 4H), 8.53-8.57 (m, 1H).

Example 58 2-[2-(3-Pyridyl)methoxyphenyl]-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one hydrochloride

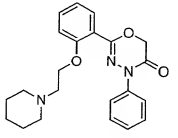


Free compound

^{1}H-NMR (400MHz, $CDCl_3$) ; δ (ppm) 4.76 (s, 2H), 5.16 (s, 2H), 7.04-7.09 (m, 2H),

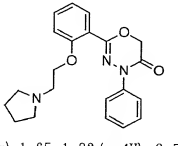
7.22 (dd, 1H), 7.24-7.29 (m, 1H), 7.34-7.40 (m, 2H), 7.44-7.50 (m, 1H), 7.59-7.64 (m, 2H), 7.66 (dd, 1H), 7.78 (ddd, 1H), 8.59 (dd, 1H), 8.69 (d, 2H).

Example 59 2-{2-[2-(1-Piperidyl)ethoxyl]phenyl}-4-phenyl-4 H-1,3,4-oxadiazine-5(6H)-one



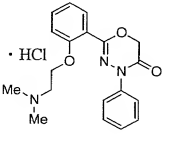
^{1}H-NMR (400MHz, $CDCl_3$) ; δ (ppm) 1.38-1.46 (m, 2H), 1.54-1.61 (m, 4H), 2.43-2.53 (m, 4H), 2.80 (t, 2H), 4.18 (t, 2H), 4.84 (s, 2H), 6.96-7.01 (m, 2H), 7.24-7.30 (m, 1H), 7.39-7.46 (m, 3H), 7.56-7.60 (m, 1H), 7.70-7.74 (m, 2H).

Example 60 2-{2-[2-(1-Pyrrolidinyl)ethoxyl]phenyl}-4-phenyl-4 H-1,3,4-oxadiazine-5(6H)-one



^{1}H-NMR (400MHz, $CDCl_3$) ; δ (ppm) 1.65-1.83 (m, 4H), 2.57-2.68 (m, 4H), 2.97 (t, 2H), 4.20 (t, 2H), 4.84 (s, 2H), 6.93 (d, 1H), 7.02 (d, 1H), 7.27 (t, 1H), 7.38-7.46 (m, 3H), 7.57-7.62 (m, 1H), 7.72 (d, 2H).

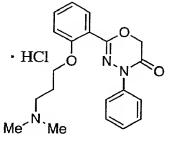
Example 61 2-[2-(2-Dimethylaminoethoxy)phenyl]-4-phenyl-4 H-1,3,4-oxadiazine-5(6H)-one hydrochloride



Free compound

^{1}H-NMR (400MHz, $CDCl_3$) ; δ (ppm) 2.31 (s, 6H), 2.76 (t, 2H), 4.13 (t, 2H), 4.83 (s, 2H), 6.97-7.03 (m, 2H), 7.25-7.30 (m, 1H), 7.40-7.46 (m, 3H), 7.59 (dd, 1H), 7.70-7.74 (m, 2H).

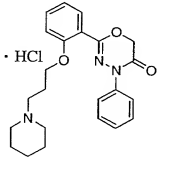
Example 62. 2-[2-(3-Dimethylaminopropoxy)phenyl]-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one hydrochloride



Free compound

^{1}H-NMR (400MHz, $CDCl_3$) ; δ (ppm) 2.00 (dd, 2H), 2.44 (t, 2H), 4.10 (t, 2H), 4.83 (s, 2H), 6.97-7.01 (m, 2H), 7.27 (t, 1H), 7.40-7.45 (m, 3H), 7.59 (dd, 1H), 7.70-7.75 (m, 2H).

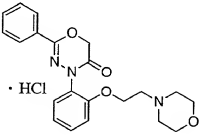
Example 63. 2-{2-[3-(1-Piperidinyl)propoxy]phenyl}-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one hydrochloride



Free compound

^{1}H-NMR (400MHz, $CDCl_3$) ; δ (ppm) 1.37-1.46 (m, 2H), 1.53-1.60 (m, 4H), 2.01 (dd, 2H), 2.30-2.40 (m, 4H), 2.46 (t, 2H), 4.08 (t, 2H), 4.83 (s, 2H), 6.95-7.00 (m, 2H), 7.27 (t, 1H), 7.39-7.46 (m, 3H), 7.58 (dd, 1H), 7.72 (d, 2H).

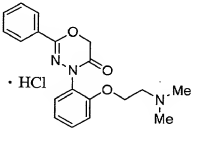
Example 64. 2-Phenyl-4-{2-[2-(4-morpholinyl)ethoxy]phenyl}-4H-1,3,4-oxadiazine-5(6H)-one hydrochloride



Free compound

^{1}H-NMR (400MHz, $CDCl_3$) ; δ (ppm) 2.40-2.56 (m, 4H), 2.74 (t, 2H), 3.50-3.60 (m, 4H), 4.18 (t, 2H), 4.89 (s, 2H), 6.99-7.04 (m, 1H), 7.06 (ddd, 1H), 7.34-7.42 (m, 4H), 7.42-7.47 (m, 1H), 7.84-7.89 (m, 2H).

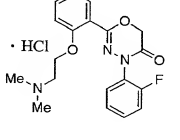
Example 65. 2-Phenyl-4-[2-(2-dimethylaminoethoxy)phenyl]-4H-1,3,4-oxadiazine-5(6H)-one hydrochloride



Free compound

^{1}H-NMR (400MHz, DMSO-d_6) ; δ (ppm) 2.09 (s, 6H), 2.52 (t, 2H), 4.06 (t, 2H), 4.96 (s, 2H), 7.03 (ddd, 1H), 7.16 (d, 1H), 7.34 (dd, 1H), 7.36-7.52 (m, 4H), 7.73-7.78 (m, 2H).

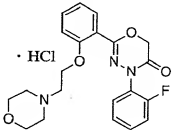
Example 66. 2-[2-(2-Dimethylaminoethoxy)phenyl]-4-(2-fluorophenyl)-4H-1,3,4-oxadiazine-5(6H)-one hydrochloride



Free compound

^{1}H-NMR (400MHz, $CDCl_3$) ; δ (ppm) 2.32 (s, 6H), 2.74 (t, 2H), 4.13 (t, 2H), 4.90 (s, 2H), 6.95-7.00 (m, 2H), 7.16-7.26 (m, 2H), 7.33-7.44 (m, 2H), 7.48-7.53 (m, 1H), 7.55 (dd, 1H).

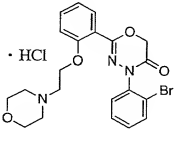
Example 67. 2-{2-[2-(4-Morpholinyl)ethoxy]phenyl}-4-(2-fluorophenyl)-4H-1,3,4-oxadiazine-5(6H)-one hydrochloride



Free compound

^{1}H-NMR (400MHz, $CDCl_3$) ; δ (ppm) 2.50-2.56 (m, 4H), 2.80 (t, 2H), 3.66-3.73 (m, 4H), 4.17 (t, 2H), 4.90 (s, 2H), 6.93-6.97 (m, 1H), 6.99 (ddd, 1H), 7.17-7.26 (m, 2H), 7.34-7.39 (m, 1H), 7.42 (ddd, 1H), 7.47-7.52 (m, 1H), 7.55 (dd, 1H).

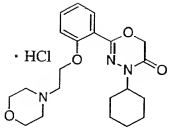
Example 68. 2-{2-[2-(4-Morpholinyl)ethoxy]phenyl}-4-(2-bromophenyl)-4H-1,3,4-oxadiazine-5(6H)-one hydrochloride



Free compound

^{1}H-NMR (400MHz, $CDCl_3$) ; δ (ppm) 2.48-2.57 (m, 4H), 2.80 (t, 2H), 3.65-3.73 (m, 4H), 4.17 (t, 2H), 4.90 (s, 2H), 6.92-6.96 (m, 1H), 6.98 (ddd, 1H), 7.27-7.31 (m, 1H), 7.38-7.44 (m, 2H), 7.48 (dd, 1H), 7.58 (dd, 1H), 7.70 (dd, 1H).

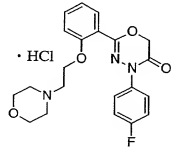
Example 69. 2-{2-[2-(4-Morpholinyl)ethoxy]phenyl}-4-cyclohexyl-4H-1,3,4-oxadiazine-5(6H)-one hydrochloride



Free compound

^{1}H-NMR (400MHz, DMSO-d_6) ; δ (ppm) 1.03-1.15 (m, 1H), 1.25-1.39 (m, 2H), 1.55-1.70 (m, 5H), 1.70-1.80 (m, 2H), 2.40-2.46 (m, 4H), 2.70 (t, 2H), 3.50-3.58 (m, 4H), 4.12 (t, 2H), 4.30-4.39 (m, 1H), 4.70 (s, 2H), 6.96-7.01 (m, 1H), 7.10-7.15 (m, 1H), 7.41-7.47 (m, 2H).

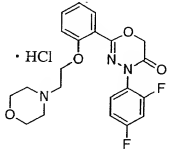
Example 70 2-{2-[2-(4-Morpholinyl)ethoxy]phenyl}-4-(4-fluorophenyl)-4H-1,3,4-oxadiazine-5(6H)-one hydrochloride



Free compound

^{1}H-NMR (400MHz, DMSO-d_6) ; δ (ppm) 2.37-2.46 (m, 4H), 2.69 (t, 2H), 3.47-3.54 (m, 4H), 4.14 (t, 2H), 4.93 (s, 2H), 7.00 (ddd, 1H), 7.15 (d, 1H), 7.23-7.30 (m, 2H), 7.45-7.50 (m, 1H), 7.54 (dd, 1H), 7.63-7.69 (m, 2H).

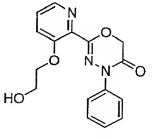
Example 71 2-{2-[2-(4-Morpholinyl)ethoxy]phenyl}-4-(2,4-difluorophenyl)-4H-1,3,4-oxadiazine-5(6H)-one hydrochloride



Free compound

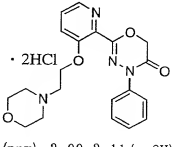
^{1}H-NMR (400MHz, DMSO-d_6) ; δ (ppm) 2.37-2.46 (m, 4H), 2.67 (t, 2H), 3.46-3.54 (m, 4H), 4.12 (t, 2H), 4.98 (s, 2H), 6.98 (ddd, 1H), 7.13 (d, 1H), 7.18-7.24 (m, 1H), 7.42-7.50 (m, 3H), 7.61 (ddd, 1H).

Example 72 2-[3-(2-Hydroxyethoxy)-2-pyridyl]-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one



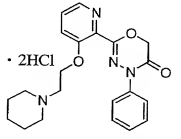
^{1}H-NMR (400MHz, $CDCl_3$) ; δ (ppm) 2.57 (t, 1H), 3.83-3.87 (m, 2H), 4.19-4.21 (m, 2H), 4.98 (s, 2H), 7.31-7.48 (m, 5H), 7.62-7.65 (m, 2H), 8.36-8.38 (m, 1H).

Example 73 2-{3-[2-(4-Morpholinyl)ethoxy]-2-pyridyl}-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one dihydrochloride



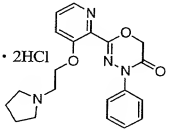
^{1}H-NMR (400MHz, DMSO-d_6) ; δ (ppm) 3.00-3.11 (m, 2H), 3.35-3.43 (m, 2H), 3.49-3.56 (m, 2H), 3.60-3.68 (m, 4H), 4.52-4.58 (m, 2H), 5.04 (s, 2H), 7.28-7.33 (m, 1H), 7.43-7.47 (m, 2H), 7.56-7.60 (m, 3H), 7.70 (dd, 1H), 8.27 (dd, 1H).

Example 74. 2-{3-[2-(1-Piperidyl)ethoxy]-2-pyridyl}-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one dihydrochloride



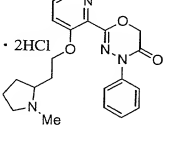
^{1}H-NMR (400MHz, DMSO-d_6) ; δ (ppm) 1.10-1.23 (m, 2H), 1.49-1.71 (m, 4H), 2.76-2.87 (m, 2H), 3.25-3.49 (m, 4H), 4.51-4.55 (m, 2H), 5.03 (s, 2H), 7.28-7.32 (m, 1H), 7.42-7.47 (m, 2H), 7.55-7.60 (m, 3H), 7.70 (dd, 1H), 8.27 (dd, 1H).

Example 75. 2-{3-[2-(1-Pyrrolidinyl)ethoxy]-2-pyridyl}-4-phenyl-4 H-1,3,4-oxadiazine-5(6H)-one dihydrochloride



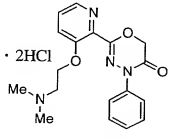
^{1}H-NMR (400MHz, DMSO-d_6) ; δ (ppm) 1.60-1.77 (m, 4H), 2.89-2.98 (m, 2H), 3.40-3.49 (m, 2H), 3.51-3.59 (m, 2H), 4.46-4.48 (m, 2H), 5.03 (s, 2H), 7.27-7.32 (m, 1H), 7.42-7.48 (m, 2H), 7.55-7.60 (m, 3H), 7.71 (dd, 1H), 8.27 (dd, 1H).

Example 76. 2-{3-[2-(1-Methyl-2-pyrrolidinyl)ethoxy]-2-pyridyl}-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one dihydrochloride



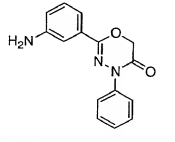
^{1}H-NMR (400MHz, DMSO-d_6) ; δ (ppm) 1.60-2.35 (m, 6H), 2.51 (s, 1.5H), 2.70 (s, 1.5H), 2.81-3.49 (m, 4H), 4.83-4.94 (m, 1H), 5.00 (s, 1H), 5.03 (s, 1H), 7.25-7.33 (m, 1H), 7.42-7.49 (m, 2H), 7.50-7.56 (m, 1H), 7.58-7.63 (m, 2H), 7.70-7.74 (m, 1H), 8.21-8.23 (m, 1H).

Example 77. 2-[3-(2-Dimethylaminoethoxy)-2-pyridyl]-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one dihydrochloride



^{1}H-NMR (400MHz, DMSO-d_6) ; δ (ppm) 2.70 (s, 3H), 2.71 (s, 3H), 3.48-3.50 (m, 2H), 3.45-3.49 (m, 2H), 5.02 (s, 2H), 7.27-7.32 (m, 1H), 7.42-7.47 (m, 2H), 7.55-7.59 (m, 3H), 7.71 (dd, 1H), 8.27 (dd, 1H).

Example 78. Synthesis of 2-(3-Aminophenyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one

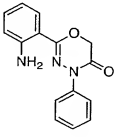


In a hydrogen atmosphere, the compound in Example 19 (417 mg) was suspended in a mixed solvent of ethanol/ethyl acetate (2:1, 24 ml), and 10 % palladium/carbon catalyst (80 mg) was added thereto, followed by stirring at room temperature for 40 minutes. After the catalyst was filtered off, the product was evaporated, and the resulting crude crystals were recrystallized from ethyl acetate/hexane, to give the title

compound (350 mg, 93 %).

^{1}H-NMR (400MHz, DMSO-d_6) ; δ (ppm) 4.93 (s, 2H), 5.28-5.32 (m, 2H), 6.65-6.69 (m, 1H), 6.97-7.01 (m, 1H), 7.06-7.11 (m, 2H), 7.27-7.32 (m, 1H), 7.42-7.48 (m, 2H), 7.62-7.66 (m, 2H).

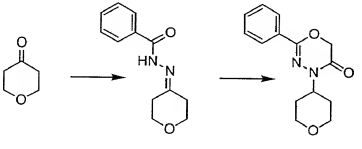
Example 79. 2-(2-Aminophenyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one



The title compound was synthesized in the same manner as in Example 78.

^{1}H-NMR (400MHz, DMSO-d_6) ; δ (ppm) 4.96 (s, 2H), 6.52-6.61 (m, 3H), 6.74-6.78 (m, 1H), 7.14-7.20 (m, 1H), 7.29-7.35 (m, 1H), 7.44-7.51 (m, 2H), 7.56-7.62 (m, 3H).

Example 80. 2-Phenyl-4-(tetrahydro-4H-pyran-4-yl)-4 H-1,3,4-oxadiazine-5(6H)-one



80-1) 4-(benzoylhydrazono)-tetrahydro-4H-pyran

Tetrahydro-4H-pyran-4-one (2.96 g) and benzoylhydrazine (4.03 g) were dissolved in ethanol (60 ml) and stirred overnight. The reaction solution was evaporated, and the resulting crude

crystals were washed with ethyl acetate, to give an imine compound (6.20 g).

^{1}H-NMR (400MHz, DMSO-d_6) ; δ (ppm) 2.37-2.45 (m, 2H), 2.46-2.54 (m, 2H), 3.66 (t, 2H), 3.72-3.80 (m, 2H), 7.42-7.49 (m, 2H), 7.50-7.57 (m, 1H), 7.76-7.85 (m, 2H), 10.57 (s, 1H).

ESI-mass ; 219 (MH^+)

80-2) 2-Phenyl-4-(tetrahydro-4H-pyran-4-yl)-4H-1,3,4-oxadiazine-5(6H)-one

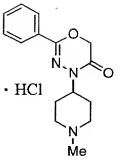
4-(Benzoylhydrazono)-tetrahydro-4H-pyran (2.50 g) obtained in 80-1) was dissolved in methanol (50 ml), and sodium borohydride (1.30 g) was added thereto under ice-cooling, followed by stirring at room temperature for 5 hours. The reaction solution was evaporated, diluted with ethyl acetate, washed with water and brine, and dried over magnesium sulfate anhydride. After the drying agent was filtered off, the filtrate was evaporated, and the resulting crude crystals were recrystallized from ethyl acetate/hexane, to give a hydrazide compound from which the title compound (1.71 g, 57 %) was obtained in the same manner as in Example 1-2.

^{1}H-NMR (400MHz, DMSO-d_6) ; δ (ppm) 1.57 (dd, 2H), 1.98 (ddd, 2H), 3.42 (t, 2H), 3.93 (dd, 2H), 4.64 (tt, 1H), 4.82 (s, 2H), 7.43-7.52 (m, 3H), 7.79-7.84 (m, 2H).

ESI-mass ; 261 (MH^+)

The following compounds in Example 81 to 83 were synthesized in the same manner as in Example 80.

Example 81. 2-Phenyl-4-(1-methyl-4-piperidyl)-4H-1,3,4-oxadiazine-5(6H)-one hydrochloride

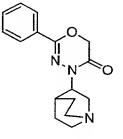


Free compound

^{1}H-NMR (400MHz, DMSO-d_6) ; δ (ppm) 1.53-1.60 (m, 2H), 1.91-2.02 (m, 4H), 2.16 (s, 3H), 2.78-2.86 (m, 2H), 4.29-4.38 (m, 1H), 4.80 (s, 2H), 7.43-7.50 (m, 3H), 7.78-7.82 (m, 2H).

ESI-mass ; 274 (MH^+)

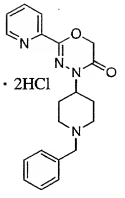
Example 82. 2-Phenyl-4-(3-quinuclidinyl)-4H-1,3,4-oxadiazine-5(6H)-one



^{1}H-NMR (400MHz, DMSO-d_6) ; δ (ppm) 1.27-1.37 (m, 1H), 1.53-1.64 (m, 2H), 1.82-1.87 (m, 1H), 1.89-1.99 (m, 1H), 2.65-2.80 (m, 3H), 2.93-3.02 (m, 1H), 3.02-3.10 (m, 1H), 3.19-3.26 (m, 1H), 4.57-4.64 (m, 1H), 4.79, 4.85 (ABq, 2H), 7.45-7.52 (m, 3H), 7.77-7.82 (m, 2H).

ESI-mass ; 286 (MH^+)

Example 83. 2-Pyridyl-4-(1-benzyl-4-piperidyl)-4H-1,3,4-oxadiazine-5(6H)-one dihydrochloride

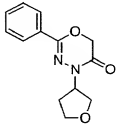


Free compound

^{1}H-NMR (400MHz, DMSO-d_6) ; δ (ppm) 1.56-1.62 (m, 2H), 1.90-2.07 (m, 4H), 2.85-2.93 (m, 2H), 3.47 (s, 2H), 4.36-4.45 (m, 1H), 4.81 (s, 2H), 7.20-7.27 (m, 1H), 7.28-7.34 (m, 4H), 7.49 (ddd, 1H), 7.87-7.95 (m, 2H), 8.63 (ddd, 1H).

ESI-mass ; 351 (MH^+)

Example 84. 2-Phenyl-4-(3-tetrahydrofuranyl)-4H-1,3,4-oxadiazine-5(6H)-one



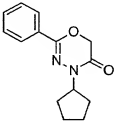
2-Phenyl-4H-1,3,4-oxadiazine-5(6H)-one (0.30 g) synthesized according to Receuil des Travaux chimiques des Pays Bas, 1929, 48, 417, 3-hydroxy tetrahydrofuran (0.30 g) and triphenyl phosphine (0.89 g) were dissolved in tetrahydrofuran (10 ml). Under ice-cooling, 40 % diethyl azodicarboxylate/toluene solution (0.59 g) diluted with tetrahydrofuran (3 ml) was added thereto, followed by stirring overnight at room temperature. The reaction solution was evaporated and purified by Cromatorex NH silica gel

chromatography (hexane/ethyl acetate system), to give the title compound (0.15 g, 36 %).

^{1}H-NMR (400MHz, DMSO-d_6) ; δ (ppm) 2.09-2.16 (m, 2H), 3.70 (dd, 1H), 3.81 (dd, 1H), 3.88-3.98 (m, 2H), 5.19-5.26 (m, 1H), 7.44-7.52 (m, 3H), 7.77-7.81 (m, 2H).

The following compounds in Example 85 to 89 were synthesized in the same manner as in Example 84.

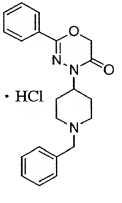
Example 85. 2-Phenyl-4-cyclopentyl-4H-1,3,4-oxadiazine-5(6H)-one



^{1}H-NMR (400MHz, $CDCl_3$) ; δ (ppm) 1.58-1.70 (m, 2H), 1.82-1.95 (m, 6H), 4.70 (s, 2H), 5.08-5.16 (m, 1H), 7.38-7.47 (m, 3H), 7.84-7.88 (m, 2H).

ESI-mass ; 245 (MH^+)

Example 86. 2-Phenyl-4-(1-benzyl-4-piperidyl)-4H-1,3,4-oxadiazine-5(6H)-one hydrochloride

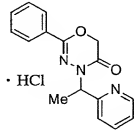


Free compound

^{1}H-NMR (400MHz, DMSO-d_6) ; δ (ppm) 1.55-1.62 (m, 2H), 1.90-2.07 (m, 4H), 2.86-2.92 (m, 2H), 3.47 (s, 2H), 4.34-4.43 (m, 1H), 4.80 (s, 2H), 7.21-7.27 (m, 1H), 7.29-

7.35 (m, 4H), 7.44-7.52 (m, 3H), 7.78-7.82 (m, 2H).

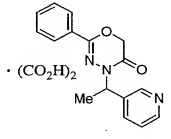
Example 87. 2-Phenyl-4-[1-(2-pyridyl)ethyl]-4H-1,3,4-oxadiazine-5(6H)-one hydrochloride



Free compound

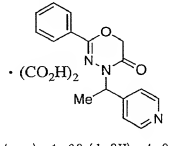
^{1}H-NMR (400MHz, $CDCl_3$) ; δ (ppm) 1.80 (d, 3H), 4.77 (s, 2H), 6.04 (q, 1H), 7.16 (t, 1H), 7.33-7.43 (m, 4H), 7.64 (t, 1H), 7.79-7.82 (m, 2H), 8.59 (d, 1H).

Example 88. 2-Phenyl-4-[1-(3-pyridyl)ethyl]-4H-1,3,4-oxadiazine-5(6H)-one oxalate



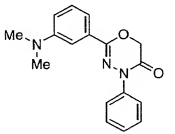
^{1}H-NMR (400MHz, DMSO-d_6) ; δ (ppm) 1.64 (d, 3H), 4.87 (s, 2H), 5.88 (q, 1H), 7.37-7.49 (m, 4H), 7.76-7.79 (m, 2H), 7.87 (d, 1H), 8.48 (d, 1H), 8.64 (s, 1H).

Example 89. 2-Phenyl-4-[1-(4-pyridyl)ethyl]-4H-1,3,4-oxadiazine-5(6H)-one oxalate



^{1}H-NMR (400MHz, DMSO-d_6) ; δ (ppm) 1.63 (d, 3H), 4.90 (s, 2H), 5.82 (q, 1H), 7.42-7.51 (m, 5H), 7.76 (d, 2H), 8.54 (d, 2H).

Example 90. 2-(3-Dimethylaminophenyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one

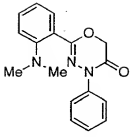


2-(3-Aminophenyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one (200 mg) obtained in Example 78 was dissolved in acetonitrile (5 ml), and 37 % aqueous formaldehyde (1 ml) and sodium cyanoborohydride (250 mg) were added thereto, and acetic acid (0.15 ml) was added dropwise thereto over 5 minute, and mixed at room temperature for 6 hours. The reaction solution was diluted with ethyl acetate, washed with an aqueous saturated sodium bicarbonate and brine, and dried over anhydrous magnesium sulfate. After the drying agent was filtered off, the filtrate was evaporated and purified by silica gel chromatography (hexane/ethyl acetate system), to give the title compound (215 mg, 97 %).

^{1}H-NMR (400MHz, DMSO-d_6) ; δ (ppm) 2.91 (s, 6H), 4.97 (s, 2H), 6.84-6.89 (m, 1H), 7.11-7.14 (m, 1H), 7.14-7.19 (m, 1H), 7.24-7.32 (m, 2H), 7.42-7.48 (m, 2H), 7.63-7.68 (m, 2H).

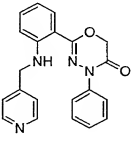
The following compounds in Example 91 to 93 were synthesized in the same manner as in Example 90.

Example 91. 2-(2-Dimethylaminophenyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one



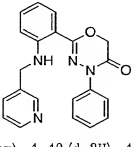
^{1}H-NMR (400MHz, DMSO-d_6) ; δ (ppm) 2.80 (s, 6H), 4.97 (s, 2H), 6.85-6.90 (m, 1H), 6.96-7.01 (m, 1H), 7.25-7.30 (m, 1H), 7.33-7.39 (m, 1H), 7.40-7.50 (m, 3H), 7.62-7.67 (m, 2H).

Example 92. 2-[2-(4-Pyridyl)methylaminophenyl]-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one



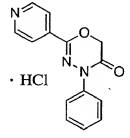
^{1}H-NMR (400MHz, DMSO-d_6) ; δ (ppm) 4.46 (d, 2H), 5.00 (s, 2H), 6.67-6.75 (m, 2H), 7.23-7.38 (m, 6H), 7.48 (d, 2H), 7.72 (dd, 1H), 7.86-7.93 (m, 1H), 8.40-8.46 (m, 2H).

Example 93. 2-[2-(3-Pyridyl)methylaminophenyl]-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one



^{1}H-NMR (400MHz, DMSO-d_6) ; δ (ppm) 4.40 (d, 2H), 4.86 (s, 2H), 6.68-6.78 (m, 2H), 7.13-7.36 (m, 5H), 7. 40-7.47 (m, 2H), 7.55-7.61 (m, 1H), 7.80-7.86 (m, 1H), 7.95-8.03 (m, 1H), 8.52-8.56 (m, 1H), 8.60 (d, 1H).

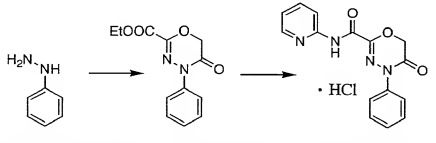
Example 94. 2-(4-Pyridyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one hydrochloride



2-(2-Chloro-4-pyridyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one hydrochloride (780 mg, 2.4 mmol) obtained in Example 12 was hydrogenated in a usual manner in methanol in the presence of sodium acetate and 10 % palladium/carbon catalyst, to give the title compound (230 mg, yield 33 %).

^{1}H-NMR (400MHz, DMSO-d_6) ; δ (ppm) 5.09 (s, 2H), 7.31-7.36 (m, 1H), 7.45-7.50 (m, 2H), 7.64-7.67 (m, 2H), 8.04 (d, 2H), 8.84 (d, 2H).

Example 95. N-(2-Pyridyl)-[4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one-2-yl]carboxamide hydrochloride



95-1) 2-ethoxycarbonyl-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one

50 g (0.366 mole) ethyl chloro-oxoacetate (ethyl oxalate chloride, (4755-77-5)) was added dropwise over 30 minutes into a solution of 39.5 g (0.365 mole) phenyl hydrazine and 50 ml triethylamine in 1000 ml tetrahydrofuran, under ice-cooling. After the dropwise addition, the mixture was stirred for 1 hour.

Then the reaction mixture was poured into water and extracted with ethyl acetate, and the organic layer was successively washed with 10 % aqueous citric acid, an aqueous sodium bicarbonate solution and a saline water, and then dried over anhydrous magnesium sulfate. The solvent was removed, and the resulting residue was crystallized from ether/hexane (1:1), collected by filtration and vacuum-dried. The resulting solid, 36 g, was dissolved in 600 ml 2-butanone, then 20.3 g (0.179 mole) chloroacetyl chloride was added thereto, followed by reacting at room temperature for 2 hours. Thereafter, the solution was heated under refluxed for further 8 hours. The reaction solution was cooled, poured into water and extracted wit ethyl acetate. The organic layer was washed with water and dried over anhydrous magnesium sulfate, and then the solvent was removed, to give an oil. It was crystallized from ethanol, to give the title compound (30 g, 0.12 mole, 33 %).

^{1}H-NMR (400MHz, $CDCl_3$) ; δ (ppm) 1. 38 (3H, t), 4. 39 (2H, q), 4. 86 (2H, s), 7. 30 (1H, t), 7. 42 (2H, t), 7. 56 (2H, d).

95-2) N-(2-Pyridyl)-[4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one-2-yl]carboxamide

970 mg (3.9 mmole) 2-ethoxycarbonyl-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one obtained in 95-1) and 900 mg (9.6 mmole) 2-aminopyridine were heated under refluxed in 10 ml methanol for 12 hours. The methanol was removed, and the resulting oil was purified by silica gel column chromatography, to give a free form of the title compound, 500 mg (1.7 mmole,

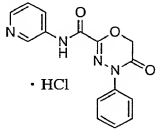
43 %). The resulting free compound was converted in a usual manner into the corresponding hydrochloride, to give the title compound.

Free compound

^{1}H-NMR (400MHz, $CDCl_3$) ; δ (ppm) 4.96 (2H, s), 7.12 (1H, dd), 7.37 (1H, t), 7.46 (2H, t), 7.58 (2H, d), 7.80 (1H, t), 8.26 (1H, d), 8.32 (1H, d), 9.21 (1H, br).

The compounds in Examples 96 and 97 were synthesized in the same manner as in Example 95.

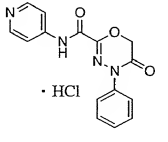
Example 96. N-(3-Pyridyl)-[4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one-2-yl]carboxamide hydrochloride



Free compound

^{1}H-NMR (400MHz, $CDCl_3$) ; δ (ppm) 4.97 (2H, s), 7.30-7.43 (2H, m), 7.50 (2H, t), 7.56 (2H, d), 8.22 (1H, d), 8.42 (1H, d), 8.68 (2H, br).

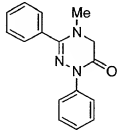
Example 97. N-(4-Pyridyl)-[4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one-2-yl]carboxamide hydrochloride



Free compound

^{1}H-NMR (400MHz, $CDCl_3$) ; δ (ppm) 4.98 (2H, s), 7.40-7.60 (7H, m), 8.57 (2H, m), 8.70 (1H, br).

Example 98. Synthesis of 1,3-diphenyl-4-methyl-4,5-dihydro-1, 2,4-triazine-6(1H)-one

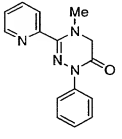


N-methylglycine ethyl ester (10 g, 0.086 mole) and 10 ml triethylamine were dissolved in 100 ml tetrahydrofuran, and 12 g (0.086 mole) benzoyl chloride was added dropwise thereinto under ice-cooling. After the mixture was returned to room temperature and stirred overnight, the reaction solution was poured into water and extracted with ethyl acetate. The organic layer was successively washed with 5 % aqueous hydrochloric acid, an aqueous sodium bicarbonate and a saline solution. The resulting solution was dried over anhydrous magnesium sulfate, and then concentrated. The resulting oil was dissolved in 300 ml tetrahydrofuran and 41 g Lawessen's reagent (CAS Registry No. 19172-47-5) was added thereto, followed by treating at room temperature for 4 hours. The reaction mixture was poured into water, extracted with ethyl acetate, washed with an aqueous sodium bicarbonate solution and brine, and dried over anhydrous magnesium sulfate. The residues were purified by silica gel column chromatography (hexane/ethyl acetate system) to give 8.0 g (0.034 mole) thioamide compound. This compound and 3.6 g (0.034 mole) phenyl hydrazine were dissolved in 50 ml ethanol and heated under reflux for 5 hours. After the solvent was

removed, the residue was dissolved in 50 ml tetrahydrofuran and 1.36 g of 60 % oily sodium hydride was added thereto, followed by treating at room temperature for 2 hours. The reaction solution was poured into ice-water, extracted with ethyl acetate, washed with water and dried. The residue obtained by concentrating it was purified by silica gel chromatography, to give the title compound, 2.4 g (0.0084 mole, 25 %).

^{1}H-NMR (400MHz, $CDCl_3$) ; δ (ppm) 3.28 (3H, s), 4.93 (2H, s), 6.67-6.80 (2H, m), 7.10-7.20 (2H, m), 7.40-7.50 (4H, m), 7.55 (2H, d).

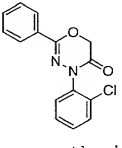
Example 99. 1-Phenyl-3-(2-pyridyl)-4-methyl-4,5-dihydro-1,2,4-triazine-6(1H)-one



The title compound was synthesized in the same manner as in Example 98.

^{1}H-NMR (400MHz, $CDCl_3$) ; δ (ppm) 3.02 (3H, s), 4.16 (2H, s), 7.24 (1H, m), 7.40 (3H, m), 7.63 (2H, d), 7.74 (1H, d), 7.83 (1H, t), 8.65 (1H, d).

Example 100. 2-Phenyl-4-(2-chlorophenyl)-4H-1,3,4-oxadiazine-5(6H)-one

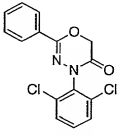


The title compound was synthesized in the same manner as

in Example 36.

^{1}H-NMR (400MHz, $CDCl_3$) ; δ (ppm) 4.95 (s, 2H), 7.35-7.43 (m, 4H), 7.44-7.51 (m, 2H), 7.51-7.55 (m, 1H), 7.86-7.91 (m, 2H).

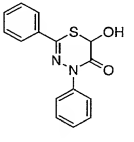
Example 101. 2-Phenyl-4-(2,6-dichlorophenyl)-4H-1,3,4-oxadiazine-5(6H)-one



The title compound was synthesized in the same manner as in Example 17.

^{1}H-NMR (400MHz, $CDCl_3$) ; δ (ppm) 4.96 (s, 2H), 7.34 (dd, 1H), 7.38-7.43 (m, 2H), 7.44-7.48 (m, 3H), 7.87-7.90 (m, 2H).

Example 102. 2,4-Diphenyl-6-hydroxy-4H-1,3,4-thiadiazine-5-one



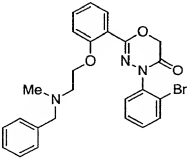
2,4-Diphenyl-4H-1,3,4-thiadiazine-5(6H)-one (150 mg) obtained in Example 4 was dissolved in trifluoroacetic acid (3 ml). Under ice-cooling, 30 % aqueous hydrogen peroxide (0.06 ml) was added dropwise thereinto, followed by stirring at room temperature for 5 hours. The reaction solution was diluted with an aqueous saturated sodium bicarbonate solution, extracted with ethyl acetate and dried over anhydrous magnesium sulfate.

After the drying agent was filtered off, the reaction solution was evaporated and purified by silica gel chromatography (hexane/ethyl acetate system), to give the title compound (10 mg, 7 %).

^{1}H-NMR (400MHz, $CDCl_3$) ; δ (ppm) 5.48 (s, 1H), 7.34-7.39 (m, 1H), 7.42-7.53 (m, 5H), 7.56-7.62 (m, 2H), 7.90-7.95 (m, 2H).

ESI-mass ; 285 (MH^+)

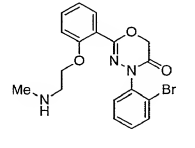
Example 103. 2-{2-[2-(N-Benzyl-N-methyl)amino]ethoxyphenyl}-4-(2-bromophenyl)-4H-1,3,4-oxadiazine-5(6H)-one



The title compound was synthesized in the same manner as in Example 54.

^{1}H-NMR (400MHz, $CDCl_3$) ; δ (ppm) 2.31 (s, 3H), 2.86 (t, 2H), 3.59 (s, 2H), 4.16 (t, 2H), 4.81 (s, 2H), 6.91-6.99 (m, 2H), 7.24-7.29 (m, 2H), 7.30-7.34 (m, 4H), 7.37-7.46 (m, 3H), 7.57 (dd, 1H), 7.68 (dd, 1H).

Example 104. 2-[2-(2-Methylamino)ethoxyphenyl]-4-(2-bromophenyl)-4H-1,3,4-oxadiazine-5(6H)-one

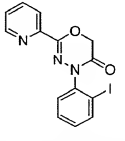


2-{2-[2-(N-Benzyl-N-methyl)amino]ethoxyphenyl}-4-(2-bromophenyl)-4H-1,3,4-oxadiazine-5(6H)-one (158 mg) obtained in Example 103 was dissolved in methanol (5 ml), and palladium hydroxide-carbon (20 mg) was added thereto, and the mixture was stirred at room temperature for 3 hours in a hydrogen atmosphere. After the palladium hydroxide-carbon was filtered off, the filtrate was evaporated, and purified by silica gel chromatography (hexane/ethyl acetate system), to give the title compound (trace).

^{1}H-NMR (400MHz, $CDCl_3$) ; δ (ppm) 2.18 (s, 3H), 3.05-3.12 (m, 2H), 4.28-4.35 (m, 2H), 4.93 (s, 2H), 6.90-7.10 (m, 2H), 7.30-7.59 (m, 4H), 7.67-7.76 (m, 2H).

ESI-mass ; 404, 406 (MH^+)

Example 105. 2-(2-Pyridyl)-4-(2-iodophenyl)-4H-1,3,4-oxadiazine-5(6H)-one

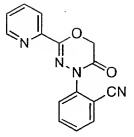


The title compound was synthesized in the same manner as in Example 1.

^{1}H-NMR (400MHz, $CDCl_3$) ; δ (ppm) 5.02 (s, 2H), 7.15 (ddd, 1H), 7.39 (ddd, 1H), 7.43-7.51 (m, 2H), 7.76 (ddd, 1H), 7.94-8.03 (m, 2H), 8.70-8.75 (m, 1H).

ESI-mass ; 280 (MH^+)

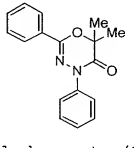
Example 106. 2-(2-Pyridyl)-4-(2-cyanophenyl)-4H-1,3,4-oxadiazine-5(6H)-one



2-(2-Pyridyl)-4-(2-iodophenyl)-4H-1,3,4-oxadiazine-5(6H)-one (100 mg) obtained in Example 105 was dissolved in N-methyl pyrrolidone (2 ml). Zinc cyanide (80 mg), copper iodide (5 mg) and tetrakis(triphenyl phosphine) palladium (10 mg) were added thereto, followed by stirring for 1 hour. The reaction solution was diluted with an aqueous saturated sodium bicarbonate solution and extracted with ethyl acetate. The organic layer was washed with water and dried over anhydrous magnesium sulfate. After the drying agent was filtered off, the reaction solution was evaporated and purified by silica gel chromatography (hexane/ethyl acetate system), to give the title compound (40 mg, 54 %).

^{1}H-NMR (400MHz, $CDCl_3$) ; δ (ppm) 5.06 (s, 2H), 7.36 (ddd, 1H), 7.44 (ddd, 1H), 7.60-7.69 (m, 2H), 7.70-7.78 (m, 2H), 7.99-8.04 (m, 1H), 8.63-8.69 (m, 1H).

Example 107 2,4-Diphenyl-6,6-dimethyl-4H-1,3,4-oxadiazine-5-one

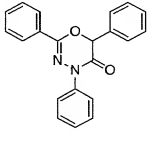


N'-phenyl-hydrazide benzoate (1 g) and triphenyl phosphine (1.48 g) were dissolved in dichloromethane (10 ml).

Under ice-cooling, 1-bromosuccinimide (1.02 g) was added thereto, followed by stirring at room temperature for 1 hour. Hexane was added to the reaction mixture, and the insoluble matters were filtered off, and the filtrate was evaporated. The resulting crude product (586 mg) was added to a mixture of ethyl 2-hydroxyisobutyrate (282 mg) and sodium hydride (104 mg) in dimethyl formamide (6 ml) under ice-cooling, followed by stirring at room temperature for 2 hours. Then, potassium tert-butoxide (50 mg) was added thereto, followed by heating under stirring at 100 °C. The reaction mixture was partitioned between ethyl acetate and water, and the organic layer was washed with water, dried and concentrated. Then, the resulting residue was purified by silica gel chromatography (ethyl acetate/hexane system), to give the title compound (31 mg) as a yellow solid.

^{1}H-NMR (400MHz, $CDCl_3$) ; δ (ppm) 1.70 (s, 6H), 7.26-7.30 (m, 1H), 7.40-7.50 (m, 5H), 7.69-7.72 (m, 2H), 7.93-7.96 (m, 2H).

Example 108. 2,4,6-triphenyl-4H-1,3,4-oxadiazine-5-one



108-(1) 2,6-Diphenyl-4H-1,3,4-oxadiazine-5-one

Mandelic acid hydrazide (1.66 g) and trimethyl o-benzoate (1.82 g) were heated under stirring in dimethyl formamide (30 ml) at 120 °C for 12 hours in the presence of p-toluene sulfonate

monohydrate (0.2 g). The solvent was evaporated, and the residue was partitioned between ethyl acetate (150 ml) and water (50 ml). The ethyl acetate layer was washed with water (50 ml x 2) and brine (50 ml), and then dried over magnesium sulfate. The solvent was evaporated, and the resulting residue was purified by silica gel chromatography (ethyl acetate/hexane, 1:1), to give the title compound as a white powder (1.28 g, 51 %).

^{1}H-NMR (400MHz, DMSO-d_6) ; δ (ppm) 6.08 (brs, 1H), 6.79 (d, 1H), 7.34 (d, 1H), 7.41 (t, 2H), 7.53 (d, 2H), 7.56-7.64 (m, 3H), 7.96 (d, 2H).

108-(2) 2,4,6-Triphenyl-4H-1,3,4-oxadiazine-5-one

A mixture of 2,6-diphenyl-4H-1,3,4-oxadiazine-5-one (0.1 g), phenyl boric acid (0.13 g), copper acetate (0.18 g) and triethylamine (0.12 g) was stirred vigorously in methylene chloride (15 ml) overnight at room temperature. The reaction solution was purified directly by silica gel chromatography (ethyl acetate/hexane, 1:2), to give the title compound as a white powder (0.048 g, 37 %).

^{1}H-NMR (400MHz, $CDCl_3$) ; δ (ppm) 6.61 (s, 1H), 7.00 (t, 1H), 7.08 (dd, 2H), 7.28 (dd, 2H), 7.37-7.54 (m, 6H), 7.65 (dd, 2H), 8.03 (dd, 2H).

Pharmacological Experimental Example 1. Inhibitory action on AMPA-inducing inflow of calcium into nerve cells

The cerebral cortex was excised from the brain of a rat on day 18 after birth and treated with trypsin and DNase, whereby the cells were dispersed. The cells were allowed to float on DMEM containing 10 % serum, inoculated into a culture bottle, and their astrocytes were grown. The astrocytes were re-

dispersed with trypsin and inoculated onto each well on a 96-well plate. After it was confirmed that the bottom of each well was completely covered with the astrocytes after culture for 1 week, cerebral cortex nerve cells dispersed in the same manner as above were inoculated thereon. After 24 hours, the medium was exchanged with fresh one, and after culture for further 1 week, the medium was exchanged with a medium containing 1 μM MK-801.

The inflow of calcium into the cells was measured using Fura2-AM that is a calcium-sensitive fluorescent pigment. By treating the cells with a Fura2-AM-containing medium for 1 hour, Fura2-AM was incorporated into the cells, and the medium was exchanged with a Tyrode solution containing 1 μM MK-801. After a test compound was added, the cells were stimulated by 2 μM AMPA. The change in the amount of calcium flowing into the cells was measured as a change in the fluorescence intensity at wavelengths of 340/380 nm. The effect of a test compound was evaluated where the reaction caused by AMPA added to the Tyrode solution free of the test compound was used as the control.

Results

Example	IC_{50} (μM)
1	11.8
3	33.2
4	12.0

6	48.0
8	21.1
10	44.2
11	69.0
12	42.8
14	1.56
15	27.5
16	24.9
17	5.83
20	28.2
22	67.3
26	10.8
27	33.1
28	25.2
29	43.5
30	1.73
31	8.3
32	36.6
33	4.28
34	9.21
35	42.7
36	2.28
37	3.94
39	51.4
40	34.8
41	53.3

42	3. 13
43	25. 3
44	22. 7
46	13. 1
48	1. 29
49	2. 70
50	27. 9
51	1. 06
52	1. 52
53	1. 92
54	4. 14
55	10. 5
56	17. 6
58	14. 3
59	8. 29
60	7. 26
61	4. 61
62	25. 1
63	24. 7
66	3. 54
67	6. 62
68	11. 1
69	68. 7
70	27. 2
71	21. 0
78	31. 8

80	62.0
86	16.9
87	25.4
88	52.3
89	54.0
90	31.4
91	19.1
94	98.7
95	48.2
100	0.8
101	3.4
102	8.2
103	4.2
104	2.7
105	1.9
106	7.3
107	6.4
108	13.2
GYKI 52466*	9.02

*; Le Peillet, et al., Brain Res., 571, 115, 1992.

Pharmacological Experimental Example 2. Inhibitory action on AMPA-inducing electric current in nerve cell membrane

The action on AMPA receptor channels was examined by a patch clamp method.

The cerebral cortex was excised from the brain of a rat

on day 18 after birth and treated with trypsin and DNase, whereby the cells were dispersed. The cells were allowed to float on DMEM containing 10 % serum, inoculated into a culture bottle, and their astrocytes were grown. The astrocytes were re-dispersed with trypsin and inoculated onto each well on a 12-well plate.

After it was confirmed that the bottom of each well was completely covered with the astrocytes after culture for 1 week, a cover glass treated with poly-l-lysine was placed thereon, and cerebral cortex nerve cells dispersed in the same manner as above were further inoculated thereon. After 24 hours, the medium was exchanged with fresh one, and after culture for further 1 week, the medium was exchanged with a medium containing 1 μM MK-801.

The membrane potential of the cerebral cortex nerve cells cultured for 9 days or more was fixed at -70 mV by a patch clamp method, and after a test compound was added, 10 μM AMPA was applied as a stimulus to the cells. By using, as the control, electric current flowing via the membrane into the cells in the absence of the test compound, the action of the compound in Example 1 was examined.

As a result, the IC_{50} value of the compound in Example 1 was 12.3 μM.

Pharmacological Experimental Example 3. Inhibitory action on AMPA-inducing spasm

A test compound or its solvent only was intravenously

injected into 4-week-old male ddy mice, and 5 minutes later, 1.5 nmol AMPA was administered into the ventricle thereby inducing spasm. The action of the test chemical was judged by the presence or absence of spasm, and its dose causing 80 % or more inhibition was regarded as an effective dose.

As a result, the inhibitory effect was demonstrated by 30 mg/kg compound in Example 1, 10 mg/kg compound in Example 14, 10 mg/kg compound in Example 36, 30 mg/kg compound in Example 54, and 30 mg/kg compound in Example 68.

Pharmacological Experimental Example 4. Action on reduction of infarct in a model with occlusion of midbrain/cerebrum arteries

The cervical region of a 8-week-old male SD rat was cut across the midline, and a right carotid artery was removed. An operation nylon thread (standard 4-0) was inserted into an external carotid artery, and blood stream in the midbrain/cerebrum arteries in the skull was occluded by the nylon thread, whereby a model with occlusion of midbrain/cerebrum arteries was prepared. Thirty minutes after the midbrain/cerebrum arteries were occluded, a test compound or its solvent only was once administered intravenously into the rat, and thereafter, it was continuously administered intravenously at a constant injection rate. The body temperature was controlled at 37.5 to 38.0° from the initiation of administration to the termination of administration. Six hours after the initiation of administration, the brain was excised from the rat and immediately cut into brain sections

of 2 mm in thickness, which were then stained with 2 % TTC solution. An image of these stained sections was incorporated into NIH image and the area of non-stained portions showing infarct loci was measured, and thereafter, the volume of the infarct loci was calculated.

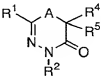
As a result, infarct loci in the cerebral cortex was reduced by 54 % and 74 % respectively in the rat given the compound in Example 1 by single intravenous administration of 6.6 mg/kg and subsequent continuous intravenous administration of 10 mg/kg/h, and by single intravenous administration of 20 mg/kg and subsequent continuous intravenous administration of 30 mg/kg/h, as compared with the rat given the solvent only.

As a compound having non-NMDA excitatory amino acid receptor antagonistic action, particularly AMPA receptor antagonistic action, the compound of the present invention, a salt thereof or hydrates thereof is useful as an agent for preventing, treating and ameliorating nerve degeneration diseases, specifically, 1) disturbance such as motor disturbance, hindrance of sensibility and abnormal behavior, caused by disturbance after cerebral ischemia and acute nerve degeneration after cerebrospinal injuries, 2) chronic nerve degeneration diseases such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis and Huntington's chorea; 3) epilepsy; 4) chronic pain, migraine, cancerous pain and pain originating in diabetic nerve disturbance; 5) spastic

paralysis; and 6) demyelinating diseases such as multiple sclerosis, encephalomyelitis, Guillain Barre syndrome, Marchiafava Bignami disease, Devic disease, Balo disease, REFSAME disease, TANGIEL disease, DEJERIN-SOTAS disease, HIV or HTLV myelopathy, and leukoencephalopathy.

Claims

1. A heterodiazinon compound represented by the following formula (I), a pharmacologically acceptable salt thereof or hydrates thereof.

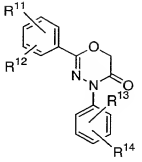


(I)

In the formula, A represents oxygen, sulfur or a group represented by the formula $>NR^3$ (wherein R^3 represents hydrogen atom or a lower alkyl group); R^1 and R^2 are the same as or different from each other and each represents an optionally substituted aryl group, an optionally substituted heteroaryl group, an optionally substituted aralkyl group, an optionally substituted heteroaryl alkyl group, an optionally substituted aryl alkenyl group, an optionally substituted heteroaryl alkenyl group, an optionally substituted piperidyl group, an optionally substituted piperazinyl group, a morpholinyl group, an optionally substituted lower cycloalkyl group, a tetrahydrofuranyl group, a tetrahydropyranyl group, an adamantyl group, an optionally substituted amino group or an optionally substituted amide group; and R^4 and R^5 are the same as or different from each other and each represents hydrogen atom, hydroxyl group, a halogen atom, nitrile group, nitro group, a lower alkyl group, an aryl group or a heteroaryl group,

provided that the compounds represented by the following

formula (II):



(II)

(wherein R^{11} and R^{12} are the same as or different from each other and each represents hydrogen atom, fluorine, chlorine, bromine, iodine, a C1-C2 fluoroalkyl group, a C1-C2 chloroalkyl group, a C1-C2 bromoalkyl group, a C1-C6 alkyl group, a C3-C6 cycloalkyl group, a C7-C9 aralkyl group, phenyl group, a C1-C6 alkoxy group, a C1-C6 alkylthio group, a C1-C6 alkylsulfinyl group, a C7-C9 aralkoxy group, phenoxy group, phenylthio group, phenylsulfonyl group, an alkali metal carboxylate C2-C5 alkoxycarbonyl group or a group represented by the formula $-N(R^{15})R^{16}$ (wherein R^{15} and R^{16} are the same as or different from each other and each represents hydrogen atom or a C1-C2 alkyl group); and R^{13} and R^{14} are the same as or different from each other and each represents a C_{1-4} alkylsulfonyl group, nitro group, a group represented by the formula $-OCH_nX_{3-n}$ (wherein X represents fluorine, chlorine, bromine or iodine; and n is an integer of 1 to 3) or the same groups as defined above for R^{11} and R^{12}) are excluded.

2. The heterodiazinon compound according to claim 1, a pharmacologically acceptable salt thereof or hydrates thereof, wherein R^4 and R^5 are the same as or different from each other

and each represents hydrogen atom, hydroxyl group, a C_{1-6} alkyl group or an aryl group.

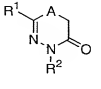
3. The heterodiazinon compound according to claim 1, a pharmacologically acceptable salt thereof or hydrates thereof, wherein R^4 is hydrogen atom and R^5 is hydroxyl group, a C_{1-6} alkyl group or an aryl group.

4. The heterodiazinon compound according to claim 1, a pharmacologically acceptable salt thereof or hydrates thereof, wherein R^4 is hydrogen atom and R^5 is hydroxyl group, methyl group, ethyl group, n-propyl group, i-propyl group or phenyl group.

5. The heterodiazinon compound according to claim 1, a pharmacologically acceptable salt thereof or hydrates thereof, wherein R^4 and R^5 are the same as or different from each other and each represents methyl group, ethyl group, n-propyl group or i-propyl group.

6. The heterodiazinon compound according to claim 1, a pharmacologically acceptable salt thereof or hydrates thereof, wherein A is oxygen.

7. The heterodiazinon compound according to claim 1, wherein R^4 and R^5 are hydrogen and which is represented by the following formula (III):



(III)

(wherein A, R^1 and R^2 have the same meanings as defined above),

a pharmacologically acceptable salt thereof or hydrates thereof.

8. The heterodiazinon compound according to claim 7, a pharmacologically acceptable salt thereof or hydrates thereof, wherein R^1 is an optionally substituted aryl group, an optionally substituted heteroaryl group, an optionally substituted aralkyl group, an optionally substituted heteroaryl alkyl group, an optionally substituted aryl alkenyl group, an optionally substituted heteroaryl alkenyl group, a morpholinyl group, a lower cycloalkyl group, an optionally substituted amino group or an optically substituted amide group; and R^2 is an optionally substituted aryl group, an optionally substituted heteroaryl group, an optionally substituted aralkyl group, an optionally substituted heteroaryl alkyl group, a lower cycloalkyl group, a tetrahydrofuranyl group, a tetrahydropyranyl group, an optionally substituted piperidyl group or an adamantyl group.

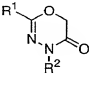
9. The heterodiazinon compound according to claim 7 or 8, a pharmacologically acceptable salt thereof or hydrates thereof, wherein the substituent groups on R^1 and R^2 are hydrogen atom, halogen atom, hydroxyl group, lower alkyl group, lower alkenyl group, lower alkynyl group, lower alkoxy group, lower thioalkoxy group, hydroxy lower thioalkoxy group, arylthio group, heteroaryl thio group, heteroaryl(hydroxy)alkyl group, halogenated lower alkyl group, hydroxy lower alkyl group, dihydroxy lower alkyl group, halogenated (hydroxy) lower alkyl

group, hydroxyalkenyl group, hydroxyalkynyl group, hydroxy lower cycloalkenyl group, lower alkoxy(hydroxy)alkyl group, lower alkoxy(hydroxy)alkoxy group, lower alkoxy alkyl group, lower alkoxy alkoxy group, lower thioalkoxy alkoxy group, lower alkyl sulfonyl alkoxy group, hydroxy lower alkoxy group, dihydroxy lower alkoxy group, hydroxy lower alkyl alkoxy group, hydroxy imino lower alkyl group, lower cycloalkyl(hydroxy)alkyl group, aralkyl group, hydroxyaralkyl group, cyano group, cyano lower alkyl group, amide group, N-lower alkyl amide group, N-lower cycloalkyl amide group, N,N-di-lower alkyl amide group, N-hydroxy lower alkyl amide group, N-hydroxy lower alkyl-N-lower alkyl amide group, N-aryl amide group, cyclic aminocarbonyl group, carbamoyl group, N-lower alkyl carbamoyl group, N,N-di-lower alkyl carbamoyl group, aminosulfonyl group, cyclic aminosulfonyl group, N-lower alkyl aminosulfonyl group, N-lower cycloalkyl aminosulfonyl group, N,N-di-lower alkyl aminosulfonyl group, N-hydroxy lower alkyl aminosulfonyl group, N-lower alkoxy alkyl aminosulfonyl group, N-halogenated lower alkyl sulfonyl group, pyrrolidinyl sulfonyl group, lower alkyl sulfonyl amino alkyl group, N-lower alkyl aminosulfonyl alkyl group, N,N-di-lower alkyl aminosulfonyl alkyl group, lower acyl group, lower acyl alkyl group, lower cycloalkyl(hydroxy)methyl group, tetrahydropyranyl group, hydroxytetrahydropyranyl group, hydroxy lower alkyl tetrahydropyranyl group, lower acyl amino alkyl group, (thiazole-2-yl)hydroxymethyl group,

di(thiazole-2-yl)hydroxymethyl group, lower alkyl sulfonyl group, lower alkoxy alkyl sulfonyl group, hydroxy lower alkyl sulfonyl group, lower alkyl sulfonyl alkyl group, N-lower alkyl amide alkyl group, aryl group, aralkyl group, heteroaryl group, heteroaryl lower alkyl group, heteroaryl lower alkoxy group, heteroaryl sulfonyl group, 4-morpholinyl sulfonyl group, 4-oxythiomorpholinyl sulfonyl group, 4-dioxythiomorpholinyl sulfonyl group, 4-morpholinyl sulfonyl group, hydroxy lower cycloalkyl group, hydroxy lower cycloalkyloxy group, hydroxy cycloalkenyl group, halogenated hydroxy lower alkyl group, 4-hydroxypiperidyl group, 4-lower alkoxypiperidyl group, ω,ω-lower alkylene dioxyalkyl group, ω,ω-lower alkylene dioxy alkoxy group, lower cycloalkyl hydroxy methyl group, aryloxy group, aryl aminosulfonyl group, amino group, lower alkyl amino group, di-lower alkyl amino group, hydroxy lower alkyl amino group, lower acyl amino group, hydroxy lower acyl amino group, lower alkyl sulfonyl amino group, pyridyl lower alkoxy group, lower alkyl pyridyl alkoxy group, lower alkoxy hydroxy alkoxy group, lower thioalkoxy alkoxy group, lower alkyl sulfonyl alkoxy group, N-lower alkyl carbamoyl group, N,N-di-lower alkyl carbamoyl group, N-hydroxy lower alkyl carbamoyl group, N-hydroxy lower alkyl-N-lower alkyl carbamoyl group, halogenated lower alkoxy group, cyano lower alkoxy group, hydroxy lower cycloalkoxy group, trifluoromethyl group, trifluoromethoxy group, amino lower alkoxy group, N-lower alkyl aminoalkoxy group, N,N-di-lower alkyl aminoalkoxy group, lower acyl alkoxy

group, lower acyl aminoalkoxy group, (1,3-dioxolanyl) lower alkyl group, (1,3-dioxolanyl) lower alkoxy group, amide lower alkoxy group, 4-(hydroxy alkyl)tetrahydropyran-4-yl group, 2,3-dihydrobenzofuranyl group, 2-hydroxy-2-alkyl-2,3-dihydrobenzofuranyl group, indanonyl group, hydroxyindanyl group, imidazolyl lower alkoxy group, succimide group or 2-oxazolidone-3-yl group, optionally substituted benzoyloxy lower alkyl group, optionally substituted amino lower alkyl group, optionally substituted amino lower alkoxy group, optionally substituted aralkyloxy group, optionally substituted heteroaryl alkoxy group, optionally substituted morpholinyl lower alkoxy group, optionally substituted piperidyl lower alkoxy group, optionally substituted piperazinyl lower alkoxy group or optionally substituted pyrrolidinyl lower alkoxy group.

10. The heterodiazinon compound according to claims 7 to 9 represented by the following formula (IV):


(IV)

(wherein R^1 and R^2 have the same meanings as defined above), a pharmacologically acceptable salt thereof or hydrates thereof.

11. The heterodiazinon compound according to claims 7 to 10, a pharmacologically acceptable salt thereof or hydrates thereof, wherein the aryl group is a group selected from phenyl

group, indenyl group, naphthyl group, azulenyl group, heptalenyl group and anthnyl group; the heteroaryl group is a group selected form thienyl group, furyl group, pyranyl group, pyrrolyl group, imidazolyl group, pyrazolyl group, triazolyl group, tetrazolyl group, isothiazolyl group, thiazolyl group, thiadiazolyl group, isoxazolyl group, pyridyl group, pyrazinyl group, pyrimidyl group, pyridazinyl group, indolizinyl group, isoindolyl group, indolyl group, indazolyl group, isoquinolyl group, quinolyl group, phthalazinyl group, naphthylidinyl group, quinoxalinyl group, quinazolinyl group and cinolynyl group; and the lower cycloalkyl group is a group selected from cyclopropyl group, cyclobutyl group, cyclopentyl group, cyclohexyl group, cycloheptyl group and cycloctyl group.

12. The heterodiazinon compound according to claims 7 to 11, which is the compound selected from the following compounds or pharmacologically acceptable salts thereof or hydrates thereof.

(1) 2-(2-Pyridyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(2) 2-(2-pyrazinyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(3) 2-(1-methyl-2-pyrolyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(4) 2,4-diphenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(5) 2-(2,3-dimethoxyphenyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(6) 2-(2-pyrrolyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(7) 2-(2-quinolyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(8) 2-(6-methyl-2-pyridyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(9) 2-benzoyloxymethyl-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(10) 2-(2-pyridyl)-4-(2,4-difluorophenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(11) 2-(2-pyridyl)-4-cyclohexyl-4H-1,3,4-oxadiazine-5(6H)-one,

(12) 2-(2-chloro-4-pyridyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(13) 2-(3-methoxy-2-pyridyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(14) 2-(3-hydroxy-2-pyridyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(15) 2-styryl-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(16) 2-[2-(3-pyridyl)vinyl]-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(17) 2-(2-methoxyphenyl)-4-(2-bromophenyl)-4H-1,3,4-oxadiazine-5 (6H)-one,

(18) 2-(4-nitrophenyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(19) 2-(3-nitrophenyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(20) 2-(2-nitrophenyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(21) 2-(4-morpholinyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-

one,

(22) 2-cyclohexyl-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(23) 2-dimethylamino-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(24) 2-dimethylamino-4-phenyl-4H-1,3,4-thiadiazine-5(6H)-one,

(25) 2-(2,6-dimethoxyphenyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(26) 2-(2-methoxyphenyl)-4-(2-fluorophenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(27) 2-phenyl-4-cyclohexyl-4H-1,3,4-oxadiazine-5(6H)-one,

(28) 2-(2-methoxyphenyl)-4-cyclohexyl-4H-1,3,4-oxadiazine-5(6H)-one,

(29) 2-(3-pyridyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(30) 2-phenyl-4-(2-bromophenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(31) 2-(2-thienyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(32) 2-benzyl-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(33) 2-(2-pyridyl)-4-(2-bromophenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(34) 2-(2-pyridyl)-4-(2-fluorophenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(35) 2-(2-pyridyl)-4-(2-methoxyphenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(36) 2-phenyl-4-(2-cyanophenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(37) 2-phenyl-4-(2-nitrophenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(38) 2-phenyl-4-(2-pyridyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(39) 2-phenyl-4-(3-pyridyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(40) 2-phenyl-4-(3-cyano-2-pyridyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(41) 2-phenyl-4-(2-hydroxymethylphenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(42) 2-phenyl-4-(2-cyano-3-pyridyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(43) 2-phenyl-4-(2-thienyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(44) 2-phenyl-4-(3-thienyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(45) 2-phenyl-4-(4-cyanophenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(46) 2-phenyl-4-(3-cyanophenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(47) 2-phenyl-4-(2-cyano-3-thienyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(48) 2-(2-hydroxyphenyl)-4-(2-bromophenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(49) 2-(2-hydroxyphenyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(50) 2-phenyl-4-(2-hydroxyphenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(51) 2-(2-hydroxyphenyl)-4-(2-fluorophenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(52) 2-(2-hydroxyphenyl)-4-(4-fluorophenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(53) 2-(2-hydroxyphenyl)-4-(2,4-difluorophenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(54) 2-[2-(2-dimethylamino)ethoxyphenyl]-4-(2-bromophenyl)-4 H-1,3,4-oxadiazine-5(6H)-one,

(55) 2-[2-(4-pyridyl)methoxyphenyl]-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(56) 2-{2-[2-(4-morpholinyl)ethoxy]phenyl}-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(57) 2-[2-(2-pyridyl)methoxyphenyl]-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(58) 2-[2-(3-pyridyl)methoxyphenyl]-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(59) 2-{2-[2-(1-piperidyl)ethoxy]phenyl}-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(60) 2-{2-[2-(1-pyrrolidinyl)ethoxy]phenyl}-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(61) 2-[2-(2-dimethylaminoethoxy)phenyl]-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(62) 2-[2-(3-dimethylaminopropoxy)phenyl]-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(63) 2-{2-[3-(1-piperidinyl)propoxy]phenyl}-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(64) 2-phenyl-{4-[2-(4-morpholinyl)ethoxy]phenyl}-4H-1,3,4-oxadiazine-5(6H)-one,

(65) 2-phenyl-4-[2-(2-dimethylaminoethoxy)phenyl]-4H-1,3,4-oxadiazine-5(6H)-one,

(66) 2-[2-(2-dimethylaminoethoxy)phenyl]-4-(2-fluorophenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(67) 2-{2-[2-(4-morpholinyl)ethoxy]phenyl}-4-(2-fluorophenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(68) 2-{2-[2-(4-morpholinyl)ethoxy]phenyl}-4-(2-bromophenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(69) 2-{2-[2-(4-morpholinyl)ethoxy]phenyl}-4-cyclohexyl-4H-1,3,4-oxadiazine-5(6H)-one,

(70) 2-{2-[2-(4-morpholinyl)ethoxy]phenyl}-4-(4-fluorophenyl)-4 H-1,3,4-oxadiazine-5(6H)-one,

(71) 2-{2-[2-(4-morpholinyl)ethoxy]phenyl}-4-(2,4-difluorophenyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(72) 2-[3-(2-hydroxyethoxy)-2-pyridyl]-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(73) 2-{3-[2-(4-morpholinyl)ethoxy]-2-pyridyl}-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(74) 2-{3-[2-(1-piperidyl)ethoxy]-2-pyridyl}-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(75) 2-{3-[2-(1-pyrrolidinyl)ethoxy]-2-pyridyl}-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(76) 2-{3-[2-(1-methyl-2-pyrrolidinyl)ethoxy]-2-pyridyl}-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(77) 2-[3-(2-dimethylaminoethoxy)-2-pyridyl]-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(78) 2-(3-aminophenyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(79) 2-(2-aminophenyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(80) 2-phenyl-4-(tetrahydro-4H-pyran-4-yl)-4H-1,3,4-oxadiazine-5(6H)-one,

(81) 2-phenyl-4-(1-methyl-4-piperidyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(82) 2-phenyl-4-(3-quinuclidinyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(83) 2-pyridyl-4-(1-benzyl-4-piperidyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(84) 2-phenyl-4-(3-tetrahydrofuranyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(85) 2-phenyl-4-cyclopentyl-4H-1,3,4-oxadiazine-5(6H)-one,

(86) 2-phenyl-4-(1-benzyl-4-piperidyl)-4H-1,3,4-oxadiazine-5(6H)-one,

(87) 2-phenyl-4-[1-(2-pyridyl)ethyl]-4H-1,3,4-oxadiazine-5(6H)-one,

(88) 2-phenyl-4-[1-(3-pyridyl)ethyl]-4H-1,3,4-oxadiazine-5(6H)-one,

(89) 2-phenyl-4-[1-(4-pyridyl)ethyl]-4H-1,3,4-oxadiazine-5(6H)-one,

(90) 2-(3-dimethylaminophenyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(91) 2-(2-dimethylaminophenyl)-4-phenyl-4H-1,3,4-

oxadiazine-5(6H)-one,

(92) 2-[2-(4-pyridyl)methylaminophenyl]-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(93) 2-[2-(3-pyridyl)methylaminophenyl]-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(94) 2-(4-pyridyl)-4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one,

(95) N-(2-pyridyl)-[4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one-2-yl]carboxamide,

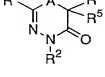
(96) N-(3-pyridyl)-[4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one-2-yl]carboxamide,

(97) N-(4-pyridyl)-[4-phenyl-4H-1,3,4-oxadiazine-5(6H)-one-2-yl]carboxamide,

(98) 1,3-diphenyl-4-methyl-4,5-dihydro-1,2,4-triazine-6(1H)-one and

(99) 1-phenyl-3-(2-pyridyl)-4-methyl-4,5-dihydro-1,2,4-triazine-6(1H)-one.

13. A pharmaceutical composition comprising a pharmacologically acceptable amount of the compound represented by the following formula (I), a pharmaceutically acceptable salt thereof or hydrates thereof, and pharmacologically acceptable carriers.



(I)

In the formula, A represents oxygen, sulfur or a group represented by the formula $>NR^3$ (wherein R^3 represents hydrogen

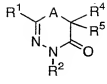
atom or a lower alkyl group); R^1 and R^2 are the same as or different from each other and each represents an optionally substituted aryl group, an optionally substituted heteroaryl group, an optionally substituted aralkyl group, an optionally substituted heteroaryl alkyl group, an optionally substituted aryl alkenyl group, an optionally substituted heteroaryl alkenyl group, an optionally substituted piperidyl group, an optionally substituted piperazinyl group, a morpholinyl group, an optionally substituted lower cycloalkyl group, a tetrahydrofuranyl group, a tetrahydropyranyl group, an adamantyl group, an optionally substituted amino group or an optionally substituted amide group; and R^4 and R^5 are the same as or different from each other and each represents hydrogen atom, hydroxyl group, halogen atom, nitrile group, nitro group, a lower alkyl group, an aryl group or a heteroaryl group,

14. The pharmaceutical composition according to claim 13, wherein R^4 and R^5 in the compound are hydrogen atoms, and the compound is represented by the following formula (V):

(V)

wherein A, R^1 and R^2 have the same meanings as defined above.

15. A pharmaceutical preparation comprising the compound represented by the following formula (I), a pharmaceutically acceptable salt thereof or hydrates thereof.



(I)

In the formula, A represents oxygen, sulfur or a group represented by the formula >NR^3 (wherein R^3 represents hydrogen atom or a lower alkyl group); R^1 and R^2 are the same as or different from each other and each represents an optionally substituted aryl group, an optionally substituted heteroaryl group, an optionally substituted aralkyl group, an optionally substituted heteroaryl alkyl group, an optionally substituted aryl alkenyl group, an optionally substituted heteroaryl alkenyl group, an optionally substituted piperidyl group, an optionally substituted piperazinyl group, a morpholinyl group, an optionally substituted lower cycloalkyl group, a tetrahydrofuranyl group, a tetrahydropyranyl group, an adamantyl group, an optionally substituted amino group or an optionally substituted amide group; and R^4 and R^5 are the same as or different from each other and each represents hydrogen atom, hydroxyl group, a halogen atom, nitrile group, nitro group, a lower alkyl group, an aryl group or a heteroaryl group,

16. The pharmaceutical preparation according to claim 15, wherein R^4 and R^5 in the compound are hydrogen atoms, and the compound is represented by formula (V):

(V)

wherein A, R^1 and R^2 have the same meanings as defined above.

17. The pharmaceutical preparation according to claim 15 or 16 for use as an agent for preventing, treating and ameliorating diseases against which non-N-methyl-D-aspartate excitatory amino acid receptor antagonistic action is effective.

18. The pharmaceutical preparation according to claim 15 or 16 for use as an agent for preventing, treating and ameliorating diseases against which 2-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor antagonistic action is effective.

19. The pharmaceutical preparation according to claim 15 or 16 for use as an agent for preventing, treating and ameliorating nerve degeneration diseases.

20. The pharmaceutical preparation according to claim 15 or 16 for use as an agent for preventing, treating and ameliorating demyelinating nerve diseases.

21. The pharmaceutical preparation according to claim 15 or 16 for use as an agent for preventing, treating and ameliorating acute nerve degeneration after cerebral ischemia, traumas in the head and spinal injuries, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, Huntington's chorea, epilepsy, pain, multiple sclerosis, encephalomyelitis, Guillain Barre syndrome, Marchiafava Bignami disease, Devic disease, Balo disease, HIV or HTLV myelopathy or leukoencephalopathy.

22. A method of preventing, treating and ameliorating diseases against which non-N-methyl-D-aspartate excitatory amino acid receptor antagonistic action is effective, which comprises administering a pharmacologically effective amount of the pharmaceutical preparation according to claim 15 or 16 to a patient.

23. A method of preventing, treating and ameliorating diseases against which 2-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor antagonistic action is effective, which comprises administering a pharmacologically effective amount of the pharmaceutical preparation according to claim 15 or 16 to a patient.

24. A method of preventing, treating and ameliorating nerve degeneration diseases, which comprises administering a pharmacologically effective amount of the pharmaceutical preparation according to claim 15 or 16 to a patient.

25. A method of preventing, treating and ameliorating demyelinating nerve diseases, which comprises administering a pharmacologically effective amount of the pharmaceutical preparation according to claim 15 or 16 to a patient.

26. A method of preventing, treating and ameliorating acute nerve degeneration after cerebral ischemia, traumas in the head and spinal injuries, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, Huntington's chorea, epilepsy, pain, multiple sclerosis, encephalomyelitis, Guillain Barre syndrome, Marchiafava Bignami disease, Devic

disease, Balo disease, HIV or HTLV myelopathy or leukoencephalopathy, which comprises administering a pharmacologically effective amount of the pharmaceutical preparation according to claim 15 or 16 to a patient.

27. Use of the compound according to claim 15 or 16 for producing an agent for preventing, treating and ameliorating diseases against which non-N-methyl-D-aspartate excitatory amino acid receptor antagonistic action is effective.

28. Use of the compound according to claim 15 or 16 for producing an agent for preventing, treating and ameliorating diseases against which 2-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor antagonistic action is effective.

29. Use of the compound according to claim 15 or 16 for producing an agent for preventing, treating and ameliorating nerve degeneration diseases.

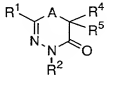
30. Use of the compound according to claim 15 or 16 for producing an agent for preventing, treating and ameliorating demyelinating nerve diseases.

31. Use of the compound according to claim 15 or 16 for producing an agent for preventing, treating and ameliorating acute nerve degeneration after cerebral ischemia, traumas in the head and spinal injuries, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, Huntington's chorea, epilepsy, pain, multiple sclerosis, encephalomyelitis, Guillain Barre syndrome, Marchiafava Bignami disease, Devic

disease, Balo disease, HIV or HTLV myelopathy or leukoencephalopathy.

Abstract

The present invention provides a novel compound having an excellent 2-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor antagonistic action, particularly a therapeutic, preventing and ameliorating action useful for cerebral ischemia, cerebrospinal injuries, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, Huntington's chorea, epilepsy, pain, spastic paralysis, multiple sclerosis etc. That is, the present invention provides a heterodiazinon compound represented by the following formula (I), a pharmacologically acceptable salt thereof or hydrates thereof.



(I)

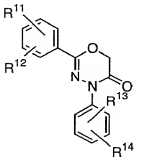
Wherein A represents an oxygen atom, a sulfur atom or a group represented by the formula >NR^3 (wherein R^3 represents hydrogen atom or a lower alkyl group);

R^1 and R^2 are the same as or different from each other and each represents an optionally substituted aryl group, an optionally substituted heteroaryl group, an optionally substituted aralkyl group, an optionally substituted heteroaryl alkyl group, an optionally substituted aryl alkenyl group, an optionally substituted heteroaryl alkenyl group, an optionally substituted piperidyl group, an optionally

substituted piperazinyl group, a morpholinyl group, an optionally substituted lower cycloalkyl group, a tetrahydrofuranyl group, a tetrahydropyranyl group, an adamantyl group, an optionally substituted amino group or an optionally substituted amide group; and

R^4 and R^5 are the same as or different from each other and each represents hydrogen atom, hydroxy, a halogen atom, nitrile group, nitro group, a lower alkyl group, an aryl group or a heteroaryl group,

provided that the compounds represented by the following formula (II):



(II)

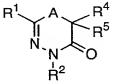
(wherein R^{11} and R^{12} are the same as or different from each other and each represents hydrogen atom, fluorine, chlorine, bromine, iodine, a C1-C2 fluoroalkyl group, a C1-C2 chloroalkyl group, a C1-C2 bromoalkyl group, a C1-C6 alkyl group, a C3-C6 cycloalkyl group, a C7-C9 aralkyl group, phenyl group, a C1-C6 alkoxy group, a C1-C6 alkylthio group, a C1-C6 alkylsulfinyl group, a C7-C9 aralkoxy group, phenoxy group, phenylthio group, phenylsulfonyl group, alkali metal carboxylate C2-C5 alkoxycarbonyl group or a group represented by the formula $-N(R^{15})R^{16}$ (wherein R^{15} and R^{16} are the same as or different from

each other and each represents hydrogen atom or a C1-C2 alkyl group); and

R^{13} and R^{14} are the same as or different from each other and each represents a C_{1-4} alkylsulfonyl group, nitro group, a group represented by the formula $-OCH_nX_{3-n}$ (wherein X represents fluorine, chlorine, bromine or iodine; and n is any of integers 1 to 3) or a group having the same meanings as the definitions of R^{11} and R^{12}) are excluded.

Abstract amended by International Search Authority

The present invention provides a hetrodiazinon compound having 2-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor antagonistic action, which is represented by the following formula (I), a pharmacologically acceptable salt thereof or hydrates thereof.



(I)

Wherein A represents O, S or a group represented by the formula NR^3 (wherein R^3 represents hydrogen atom or a lower alkyl group);

R^1 and R^2 are the same as or different from each other and each represents an optionally substituted (hetero)aryl group etc.; and

R^4 and R^5 are the same as or different from each other and each represents hydroxy, a halogen atom, nitrile group, nitro group, a lower alkyl group, a (hetero)aryl group etc.

BIRCH STEWART, KOLASCH & BIRCH, LLP

PLEASE NOTE: YOU MUST COMPLETE THE FOLLOWING:

COMBINED DECLARATION AND POWER OF ATTORNEY

FOR PATENT AND DESIGN APPLICATIONS

ATTORNEY DOCKET NO. 0425-0847P

As a below named inventor, I hereby declare that: my residence, post office address and citizenship are as stated next to my name; that I verily believe that I am the original, first and sole inventor (if only one inventor is named below) or an original, first and joint inventor (if plural inventors are named below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

Insert Title: Heterodiazinon compound

Fill in Appropriate Information - For Use Without Specification Attached:

the specification of which is attached hereto. If not attached hereto,

the specification was filed on _____ as

United States Application Number _____; and /or

the specification was filed on Feb. 15, 2000 as PCT

International Application Number PCT/JP00/0799; and was

amended under PCT Article 19 on _____ (if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

I do not know and do not believe the same was ever known or used in the United States of America before my or our invention thereof, or patented or described in any printed publication in any country before my or our invention thereof or more than one year prior to this application, that the same was not in public use or on sale in the United States of America more than one year prior to this application, that the invention has not been patented or made the subject of an inventor's certificate issued before the date of this application in any country foreign to the United States of America on an application filed by me or my legal representatives or assigns more than twelve months (six months for designs) prior to this application, and that no application for patent or inventor's certificate on this invention has been filed in any country foreign to the United States of America prior to this application by me or my legal representatives or assigns, except as follows.

I hereby claim foreign priority benefits under Title 35, United States Code, §119 (a)-(d) of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Insert Priority Information: (if appropriate)

Prior Foreign Application(s)			Priority Claimed	
11-36233 (Number)	Japan (Country)	Feb. 15, 1999 (Month/Day/Year Filed)	☒ Yes	☐ No
(Number)	(Country)	(Month/Day/Year Filed)	☐ Yes	☐ No
(Number)	(Country)	(Month/Day/Year Filed)	☐ Yes	☐ No
(Number)	(Country)	(Month/Day/Year Filed)	☐ Yes	☐ No
(Number)	(Country)	(Month/Day/Year Filed)	☐ Yes	☐ No

Insert Provisional Application(s): (if any)

I hereby claim the benefit under Title 35, United States Code, §119(e) of any United States provisional application(s) listed below.

(Application Number) (Filing Date)

(Application Number) (Filing Date)

Insert Requested Information: (if appropriate)

All Foreign Applications, if any, for any Patent or Inventor's Certificate Filed More Than 12 Months (6 Months for Designs) Prior To The Filing Date of This Application:

Country	Application No	Date of Filing (Month/Day/Year)

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application:

Insert Prior U.S. Application(s): (if any)

(Application Number) (Filing Date) (Status - patented, pending, abandoned)

(Application Number) (Filing Date) (Status - patented, pending, abandoned)

I hereby appoint the following attorneys to prosecute this application and/or an international application based on this application and to transact all business in the Patent and Trademark Office connected therewith and in connection with the resulting patent based on instructions received from the entity who first sent the application papers to the attorneys identified below, unless the inventor(s) or assignee provides said attorneys with a written notice to the contrary:

Terrell C. Birch	(Reg. No. 19,382)	Raymond C. Stewart	(Reg. No. 21,066)
Joseph A. Kolasch	(Reg. No. 22,463)	James M. Slattery	(Reg. No. 28,380)
Bernard L. Sweeney	(Reg. No. 24,448)	Michael K. Mutter	(Reg. No. 29,680)
Charles Gorenstein	(Reg. No. 29,271)	Gerald M. Murphy, Jr.	(Reg. No. 28,977)
Leonard R. Svensson	(Reg. No. 30,330)	Terry L. Clark	(Reg. No. 32,644)
Andrew D. Meikle	(Reg. No. 32,868)	Marc S. Weiner	(Reg. No. 32,181)
Joe McKinney Muncy	(Reg. No. 32,334)	Andrew F. Reish	(Reg. No. 35,443)
C. Joseph Faraci	(Reg. No. 32,350)	Donald J. Daley	(Reg. No. 34,313)

Send Correspondence to: **BIRCH, STEWART, KOLASCH & BIRCH, LLP**

P.O. Box 747 • Falls Church, Virginia 22040-0747

Telephone: (703) 205-8000 • Facsimile: (703) 205-8050

PLEASE NOTE: YOU MUST COMPLETE THE FOLLOWING:

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

1-00 **Full Name of First or Sole Inventor: Insert Name of Inventor Insert Date This Document is Signed**

GIVEN NAME / FAMILY NAME	INVENTOR'S SIGNATURE	DATE*
Koichi ITO	Koichi Ito	July 24, 2001
Residence (City, State & Country)		**CITIZENSHIP**
Chiba, Japan JPX		Japanese
POST OFFICE ADDRESS (Complete Street Address including City, State & Country)		
1-20-1-205, Tennodai, Abiko-shi, Chiba, Japan		

Insert Residence Insert Citizenship ➡ **Insert Post Office Address** ➡

2-00 **Full Name of Second Inventor, if any**

GIVEN NAME / FAMILY NAME	INVENTOR'S SIGNATURE	DATE*
Noritaka KITAZAWA	N. Kitazawa	July 24, 2001
Residence (City, State & Country)		**CITIZENSHIP**
Ibaraki, Japan JPX		Japanese
POST OFFICE ADDRESS (Complete Street Address including City, State & Country)		
5-5-23, Higashi, Toride-shi, Ibaraki, Japan		

see above

3-00 **Full Name of Third Inventor, if any**

GIVEN NAME / FAMILY NAME	INVENTOR'S SIGNATURE	DATE*
Satoshi NAGATO	S. Nagato	July 24, 2001
Residence (City, State & Country)		**CITIZENSHIP**
Chiba, Japan JPX		Japanese
POST OFFICE ADDRESS (Complete Street Address including City, State & Country)		
2037-1-201, Matsudo, Matsudo-shi, Chiba, Japan		

see above

4-00 **Full Name of Fourth Inventor, if any**

GIVEN NAME / FAMILY NAME	INVENTOR'S SIGNATURE	DATE*
Akiharu KAJIWARA	A. Kajiwara	July 24, 2001
Residence (City, State & Country)		**CITIZENSHIP**
Ibaraki, Japan JPX		Japanese
POST OFFICE ADDRESS (Complete Street Address including City, State & Country)		
6-4, Inarimae, Tsukuba-shi, Ibaraki, Japan		

see above

5-00 **Full Name of Fifth Inventor, if any**

GIVEN NAME / FAMILY NAME	INVENTOR'S SIGNATURE	DATE*
Tatsuto FUKUSHIMA	T. Fukushima	July 24, 2001
Residence (City, State & Country)		**CITIZENSHIP**
Ibaraki, Japan JPX		Japanese
POST OFFICE ADDRESS (Complete Street Address including City, State & Country)		
1-11-17-302, Matsushiro, Tsukuba-shi, Ibaraki, Japan		

see above

* DATE OF SIGNATURE

6-00

Full Name of Sixth Inventor:
Insert Name of Inventor
Insert Date This Document is Signed
Insert Residence
Insert Citizenship

GIVEN NAME FAMILY NAME	INVENTOR'S SIGNATURE	*DATE
Shinji HATAKEYAMA	Shinji Hatakeyama	July 24, 2001
RESIDENCE (City, State & Country)		CITIZENSHIP
Ibaraki, Japan JPX		Japanese
POST OFFICE ADDRESS (Complete Street Address including City, State & Country)		
2-25-9-301, Matsushiro, Tsukuba-shi, Ibaraki, Japan		

Insert Post Office Address

7-00

Full Name of Seventh Inventor, If any:
see above

GIVEN NAME FAMILY NAME	INVENTOR'S SIGNATURE	*DATE
Takahisa HANADA	T. Hanada	July 24, 2001
RESIDENCE (City, State & Country)		CITIZENSHIP
Ibaraki, Japan JPX		Japanese
POST OFFICE ADDRESS (Complete Street Address including City, State & Country)		
2-33-3, Sakura, Tsukuba-shi, Ibaraki, Japan		

8-00

Full Name of Eighth Inventor, If any:
see above

GIVEN NAME FAMILY NAME	INVENTOR'S SIGNATURE	*DATE
Masataka UENO	Masataka Ueno	July 24, 2001
RESIDENCE (City, State & Country)		CITIZENSHIP
Ibaraki, Japan JPX		Japanese
POST OFFICE ADDRESS (Complete Street Address including City, State & Country)		
7-20-6, Mizukino, Moriyamachi, Kitasouma-gun, Ibaraki, Japan		

9-00

Full Name of Nineth Inventor, If any:
see above

GIVEN NAME FAMILY NAME	INVENTOR'S SIGNATURE	*DATE
Kohshi UENO	Kohshi Ueno	July 24, 2001
RESIDENCE (City, State & Country)		CITIZENSHIP
Ibaraki, Japan JPX		Japanese
POST OFFICE ADDRESS (Complete Street Address including City, State & Country)		
668-49, Shimohirooka, Tsukuba-shi, Ibaraki, Japan		

10-00

Full Name of Tenth Inventor, If any:
see above

GIVEN NAME FAMILY NAME	INVENTOR'S SIGNATURE	*DATE
Koki KAWANO	Koki KAWANO	July 24, 2001
RESIDENCE (City, State & Country)		CITIZENSHIP
Ibaraki, Japan JPX		Japanese
POST OFFICE ADDRESS (Complete Street Address including City, State & Country)		
2-1-7-201, Umezono, Tsukuba-shi, Ibaraki, Japan		

Full Name of Eleventh Inventor, If any:
see above

GIVEN NAME FAMILY NAME	INVENTOR'S SIGNATURE	*DATE
RESIDENCE (City, State & Country)		CITIZENSHIP
POST OFFICE ADDRESS (Complete Street Address including City, State & Country)		

Full Name of Twelveth Inventor, If any:
see above

GIVEN NAME FAMILY NAME	INVENTOR'S SIGNATURE	*DATE
RESIDENCE (City, State & Country)		CITIZENSHIP
POST OFFICE ADDRESS (Complete Street Address including City, State & Country)		

Full Name of Thirteen Inventor, If any:
see above

GIVEN NAME FAMILY NAME	INVENTOR'S SIGNATURE	*DATE
RESIDENCE (City, State & Country)		CITIZENSHIP
POST OFFICE ADDRESS (Complete Street Address including City, State & Country)		

*Note: Must be completed — date this document is signed.